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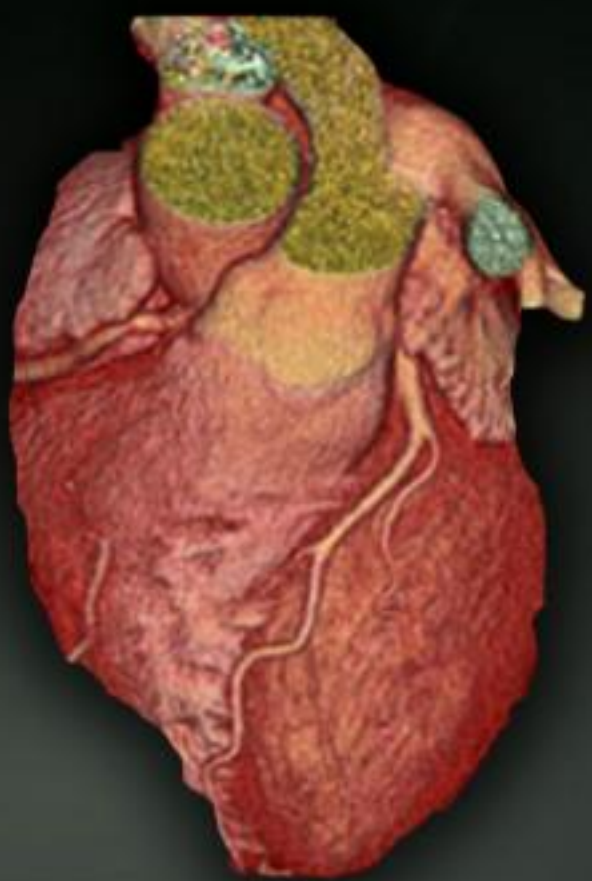
ACUTE CORONARY SYNDROMES

A Companion to BRAUNWALD'S HEART DISEASE



SECOND EDITION

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Acute Coronary Syndromes

A Companion to Braunwald's Heart Disease

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A Companion to Braunwald's Heart Disease

Pierre Théroux, MD
Professor of Medicine
University of Montreal
Montreal, Canada

Head Coronary Care Unit
Montreal Heart Institute
Montreal, Canada

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

ACUTE CORONARY SYNDROMES, SECOND EDITION ISBN: 978-1-4160-4927-2

Acute coronary syndromes : a companion to Braunwald's heart disease / [edited by] Pierre Theroux.—2nd ed.
p. ; cm.
Companion to: Braunwald's heart disease / edited by Peter Libby … [et al.]. 8th ed. c2008.
Includes bibliographical references and index.
ISBN 978-1-4160-4927-2
1. Coronary heart disease. I. Théroux, Pierre. II. Braunwald's heart disease.
[DNLM: 1. Acute Coronary Syndrome. WG 300 A185884 2011]
RC685.C6A288 2011
616.1′23—dc22 2010021019

Executive Publisher: Natasha Andjelkovic
Editorial Assistant: Bradley McIlwain
Publishing Services Manager: Catherine Jackson
Senior Project Manager: Mary Pohlman
Design Manager: Steven Stave

Printed in United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To

Doris

Julie, Martin, and Nelly

Marie Josée, Michel, Audrey, and Philippe

Contributors

Joseph S. Alpert, MD
Professor of Medicine
Head, Department of Medicine
University of Arizona Health Science Center
Tucson, Arizona

Jeffrey L. Anderson, MD, FACC, FAHA
Intermountain Healthcare Hospitals
Salt Lake City, Utah

Elliott M. Antman, MD
Brigham and Women's Hospital, Cardiovascular Division
TIMI Study Group
Boston, Massachusetts

Nipun Arora, MD
University of Missouri-Columbia
Columbia, Missouri

Jean-Pierre Bassand, MD
Cardiology Department
University Hospital Besançon
Besançon, France

Shannon M. Bates, MD, CM
Department of Medicine
McMaster University
Henderson Research Centre
Hamilton, Ontario, Canada

Richard C. Becker, MD
Divisions of Cardiology and Hematology
Duke University Medical Center
Cardiovascular Thrombosis Center
Duke Clinical Research Institute
Durham, North Carolina

Jacob Fog Bentzon, MD, PhD
Atherosclerosis Research Unit
Department of Cardiology
Aarhus University Hospital, Skejby, Brendstrupgaardsvej
Aarhus, Denmark

Deepak L. Bhatt, MD
Associate Director
Cleveland Clinic Cardiovascular Coordinating Center
Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Olivier Blanc-Brude, PhD
Cardiovascular Research Center Inserm-Lariboisière
Hôpital Lariboisière
Paris, France

Eugene Braunwald, MD
Brigham and Women's Hospital, Cardiovascular Division
TIMI Study Group
Department of Medicine
Harvard Medical School
Boston, Massachusetts

Ralph G. Brindis, MD, MPH
Oakland Medical Center
Oakland, California

Kenneth A. Brown, MD
Professor of Medicine and Cardiology
Professor of Radiology
University of Vermont College of Medicine
Burlington, Vermont

Christopher P. Cannon, MD
Brigham and Women's Hospital
TIMI Study Group
Boston, Massachusetts

Bernard R. Chaitman, MD, FACC
Department of Medicine
Division of Cardiology
Saint Louis University School of Medicine
St. Louis, Missouri

Wai-Hong Chen, MBBS
Division of Cardiology, Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

Clara Kayei Chow, MBBS, FRACP, PhD
Director, Population Health Research Institute
Hamilton General Hospital
Hamilton, Ontario, Canada

Kuang-Yuh Chyu, MD, PhD
Division of Cardiology and Atherosclerosis Research Center
Cedars-Sinai Heart Institute
Los Angeles, California

Patrick Commerford, MBChB, FCP(SA)
Professor of Cardiology
Department of Medicine
University of Cape Town
Cape Town, South Africa

Simon de Denus, BPharm, MSc
Assistant Professor, Faculty of Pharmacy
Université de Montréal, Department of Pharmacy
Montreal Heart Institute
Montreal, Quebec, Canada

Pim J. de Feyter, MD, PhD, FACC
Erasmus MC
Rotterdam, The Netherlands

Michel de Lorgeril, MD
Faculty of Medicine
Domaine de la Merci
University of Grenoble
La Tronche, France

Leonardo De Luca, MD, PhD
Department of Cardiovascular Sciences
Laboratory of Interventional Cardiology
European Hospital
Rome, Italy

Ariel Diaz, MD, MSc
Department of Medicine
Université de Montreal
Montreal Heart Institute
Montreal, Quebec, Canada

Anique Ducharme, MD, MSc
Department of Medicine
Université de Montreal
Montreal Heart Institute
Montreal, Quebec, Canada

Erling Falk, MD, PhD
Atherosclerosis Research Unit
Department of Cardiology
Aarhus University Hospital, Skejby, Brendstrupgaardsvej
Aarhus, Denmark

Richard Gallo, MD, FRCPC, FACC
Interventional Cardiologist
Montreal Heart Institute;
Associate Professor of Medicine
University of Montreal
Montreal, Quebec, Canada

Anselm K. Gitt, MD
Institut fuer Herzinfarktforschung Ludwigshafen an der Universitaet Heidelberg
Heidelberg, Germany

Christopher B. Granger, MD
Duke Clinical Research Institute and the Division of Cardiology
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Paul Gurbel, MD
Sinai Center for Thrombosis Research
Sinai Hospital of Baltimore
Baltimore, Maryland

Christian W. Hamm, MD, FACC
Medical Director
Kerckhoff Heart Center
Bad Nauheim, Germany

David Hasdai, MD
Intensive Cardiac Care Unit
Rabin Medical Center
Petah Tikva, Israel

Allan S. Jaffe, MD
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

E. Marc Jolicoeur, MD, MSc
Assistant Profesor of Medicine
Université de Montréal
Montreal, Quebec, Canada

Martin Juneau, MD
Co-president, Cardiologist and Manager of Prevention
Montreal Heart Institute
Montreal, Quebec, Canada

Jason N. Katz, MD
Duke Clinical Research Institute and the Division of Cardiology
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Catherine Labbé, MSc
Université de Montréal
Montreal Heart Institute
Montreal, Quebec, Canada

Jennifer Lash, MD
Department of Medicine
Division of Cardiology
Saint Louis University School of Medicine
St. Louis, Missouri

Peter Libby, MD
Brigham and Women's Hospital
Cardiovascular Division
Boston, Massachusetts

Jens Lohrmann, MD
Division of Cardiology
Universitäts of Freiburg
Freiburg, Germany

Telly A. Meadows, MD
Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Jessica L. Mega, MD, MPH
Brigham and Women's Hospital, Cardiovascular Division
TIMI Study Group
Boston, Massachusetts

Shamir R. Mehta, MD, MSc, FRCPC
Director, Interventional Cardiology and Acute Coronary Syndrome Research Program
Population Health Research Institutes
Hamilton Health Sciences
McMaster Clinic
Hamilton, Ontario, Canada

L. Kristin Newby, MD, MHS
Duke Clinical Research Institute and the Division of Cardiology
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Koen Nieman, MD
Erasmus MC
Rotterdam, The Netherlands

Anil Nigam, MD
Chief, Clinical Care Service
Montreal Heart Institute
Montreal, Quebec, Canada

Lionel H. Opie, MD, DPhil, DSc, FRCP
Professor of Medicine Emeritus
Director, Hatter Institute for Cardiology Research
Department of Medicine
University of Cape Town
Cape Town, South Africa

Michael S. Phillips, PhD
Associate Professor, Faculty of Medicine
Université de Montréal
Montreal Heart Institute
Montreal, Quebec, Canada

Nicolo Piazza, MD, FRCPC
Visiting Research Fellow, Thoraxcenter
Rotterdam, The Netherlands

Jonathan P. Piccini, MD
Duke Clinical Research Institute and the Division of Cardiology
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Sunil V. Rao, MD
The Duke Clinical Research Institute
Durham, North Carolina

John D. Rioux, PhD
Associate Professor, Faculty of Medicine
Université de Montréal
Montreal Heart Institute
Montreal, Quebec, Canada

Marc S. Sabatine, MD, MPH
Brigham and Women's Hospital, Cardiovascular Division
TIMI Study Group
Boston, Massachusetts

Patricia Salen, BSc
University of Grenoble
La Tronche, France

Jon-David R. Schwalm, MD, FRCPC
Department of Medicine
Division of Cardiology
McMaster University
Hamilton, Ontario, Canada

Prediman K. Shah, MD
Director, Division of Cardiology
Cedars-Sinai Medical Center
Los Angeles, California

Daniel I. Simon, MD
University Hospitals Harrington-McLaughlin Heart & Vascular Institute
University Hospitals Case Medical Center
Case Cardiovascular Center
Case Western Reserve University School of Medicine
Cleveland, Ohio

P. Gabriel Steg, MD
Département de Cardiologie
Hôpital Bichat-Claude Bernard
Paris, France

Jean-Claude Tardif, MD
Professor, Faculty of Medicine
Université de Montréal
Montreal Heart Institute
Montreal, Quebec, Canada

Michael W. Tempelhof, MD
Northwestern University Medical Center
Chicago, Illinois

Koon K. Teo, MBBCh, PhD, FRCPI, FRCPC
Professor, Department of Medicine (Cardiology)
Associate Member, Dept of Clinical Epidemiology & Biostatistics
Hamilton General Hospital
Hamilton, Ontario, Canada

Udho Thadani, MD, MRCP, FRCPC, FACC, FAHA
Professor Emeritus (Active) of Medicine
Cardiovascular Section
University of Oklahoma Health Sciences Center;
Staff Cardiologists
VA Medical Center
Oklahoma City, Oklahoma

Pierre Théroux, MD
Professor of Medicine
University of Montreal;
Head, Coronary Care Unit
Montreal Heart Institute
Montreal, Quebec, Canada

Peter L. Thompson, MD, FRACP, FACC, FACP
Cardiologist
Sir Charles Gairdner Hospital;
Clinical Professor of Medicine and Population Health
University of Western Australia
Nedlands, Australia

Kristian Thygesen, MD, DSc
Department of Medicine and Cardiology
Aarhus University Hospital, Tage-Hansens
Aarhus, Denmark

Fabrizio Tomai, MD, FACC, FESC
Department of Cardiovascular Sciences
Laboratory of Interventional Cardiology
European Hospital
Rome, Italy

Lars Wallentin, MD, PhD
Professor of Cardiology
Director Uppsala Clinical Research Centre
Uppsala Clinical Research Centre and Department Cardiology
University Hospital
Uppsala, Sweden

Jeffrey I. Weitz, MD
Department of Medicine
McMaster University
Henderson Research Centre
Hamilton, Ontario, Canada

Harvey D. White, DSc
Director, Coronary Care and Cardiovascular Research
Green Lane Hospital
Auckland, New Zealand

Salim Yusuf, DPhil, FRCPC, FRSC
Professor of Medicine
Director, Population Health Research Institute
Vice President Research and Chief Scientific Officer
Hamilton Health Sciences
McMaster University
Heart and Stroke Foundation Endowed Chair in Cardiovascular Research
Hamilton General Hospital
Hamilton, Ontario, Canada

Foreword

At the beginning of the 20th century, coronary artery disease was considered to be a serious condition but the distinction between its two principal presentations, angina pectoris and acute myocardial infarction, was not clear. By the 1920s, the separate clinical and pathological manifestation of chronic angina pectoris and acute myocardial infarction had been established and their differences recognized. In the 1930s a condition characterized by prolonged chest pain that sometimes led to acute myocardial infarction was described, and by the 1940s a syndrome intermediate between angina pectoris and acute myocardial infarction, the so-called "intermediate syndrome" was deemed to be quite common. In the early 1970s, the term unstable angina was coined and we now consider this designation to include patients with the new onset of severe angina, patients with accelerated angina, and those with angina at rest but without evidence of myocardial necrosis.

As unstable angina became more clearly defined, increasing attention was directed to the separation of patients with acute myocardial infarction into those who presented with and those without electrocardiographic ST segment elevation. It then became apparent that patients with unstable angina actually had or frequently developed the latter condition, that is, non–ST segment elevation myocardial infarction (NSTEMI).

By the 1990s, with the development of more sensitive biochemical markers of myocardial necrosis, the distinction between unstable angina and NSTEMI again became blurred. Indeed, an increasing percentage of patients with the former condition were shown actually to have the latter. By the end of the 20th century, it became clear that from both pathophysiologic and clinical points of view that these two conditions should be considered together and they are now commonly referred to as non–ST segment elevation acute coronary syndromes (NSTE-ACS).

Research on acute coronary syndromes has exploded on many fronts and this impressive second edition of *Acute Coronary Syndromes,* edited by Pierre Théroux, masterfully captures the major developments. It carefully explores the many epidemiologic, clinical, pathophysiologic, and therapeutic advances in the field. The enormous frequency of this condition and its seriousness places it at "the heart" of cardiology. Indeed, just about every adult cardiologist—whether an invasive or a non-invasive cardiologist, whether primarily office- or hospital-based, whether specializing in hypertension, heart failure, prevention, or rehabilitation—encounters patients with acute coronary syndromes and must be comfortable with their diagnosis and management.

Cardiologists dealing with these patients will be indebted to Dr. Théroux, an experienced clinician and investigator in this field, and his talented authors for providing this important new book. We are proud that it is a companion to *Braunwald's Heart Disease—A Textbook of Cardiovascular Medicine.*

Eugene Braunwald
Boston, Massachusetts

Robert O. Bonow
Chicago, Illinois

Peter Libby
Boston, Massachusetts

Douglas L. Mann
St. Louis, Missouri

Douglas P. Zipes
Indianapolis, Indiana

Preface

The first edition of this text was published in 2003 when acute coronary syndrome had become a well-defined clinical entity decades after clinical observations on premonitory symptoms preceding myocardial infarction and sudden death. The syndrome demarcates the acute unstable life-threatening manifestations of coronary atherosclerosis from the silent/stable manifestations of the disease. The bridge between the two conditions is the unstable plaque; diagnostic clues to the presence of such plaques are progressive angina, ST-T changes, and cardiac troponin elevation, all indicators of evolving ischemia. The opportunity to recognize patients at risk and prevent myocardial infarction and cardiac death set the stage for a wealth of fundamental and clinical research on the epidemiology and pathophysiology of dynamic atherosclerosis. It set a model for testing interventions aimed at preventing progression of the disease taking profit from the art of clinical trials being in full expansion. The sample size and event rates were there. Patients with chest pain and acute coronary syndromes indeed populated emergency departments and coronary care units, carrying a high-risk of acute ischemic events and recurrence of an event in the following months. Accordingly, the first edition of this text was mainly didactic and focused on prevalence, pathophysiology, diagnostic methods, and medical management and interventional procedures. It also included coverage of subgroups, secondary prevention, and guidelines recommendations for management.

Seven years later, we have reached a very different stage. As stated by Dr. Braunwald in a recent introduction to the latest edition of *Braunwald's Heart Disease*, *"the exponential growth curve of new knowledge has never been steeper and the new edition of Braunwald's Heart Disease has been created to meet that challenge."* The second edition of this companion text on *Acute Coronary Syndromes,* shares the same objective. New materials added include observations from recent large prospective registries, data obtained using new antithrombotic and antiplatelet drugs, the expanding use of invasive management worldwide in part by creation of transfer networks, recent guidelines recommendations, and the coronary care unit on the move. Other trends include an increasing number of innovative drugs, an international collaboration for testing intervention safety and efficacy, and wide online access to information, educational material and results of clinical trials, all promoting universal standards in the quality of care. To a certain extent, the progress in basic science conducted in parallel and apparent chaos with innovations converges in a regression to the more fundamental mechanisms and laws of nature. Thus, advances in genetics, pharmacology, hematology, immunology, and technology are all integrated throughout this text.

Acute Coronary Syndromes is aimed at physicians, trainees, and scientists with an interest in general cardiology and atherosclerosis. The format and content of this edition are different from the previous one. Clinically relevant content has been reinforced and more recent and thought-provoking material added. The new chapters shed new light on the present and into the near future.

The second edition consists of five sections with different perspectives. The first is a population-based vision of atherosclerosis and acute coronary syndromes. Epidemiological and clinical data recently acquired from large prospective international, European, and American registries are presented. Most importantly, the risk factor profiles that precede the first myocardial infarction in different parts of the world are described as well as the recently observed shifts in risk factors, disease presentation, treatment and prognosis, and on treatment gaps that are still present. A disease-based perspective is found in Section II. It starts with two updated classic topics and moves to less understood pathophysiologies, and ends with pharmacogenomics, a must in new medicine. Section III is a patient-based perspective reviewing the available diagnostic tools in acute coronary syndromes. The section starts with clinical recognition and moves to discuss biomarkers, a topic particularly relevant in the context of the new universal definition of myocardial infarction and the emergence of high-sensitivity troponin assays. Specific diagnostic technologies are then discussed; echocardiography, computed tomography, nuclear and magnetic resonance imaging, and more experimental techniques attempting to identify culprit coronary lesions. The various pieces for risk stratification are then put together to the benefit of clinicians. Section IV is all about therapy, starting with a review of basic medical management with anti-platelet and anticoagulant therapy, anti-ischemic therapy, and a view on new emerging drugs. Important specific issues are then considered including plaque passivation, drug resistance, bleeding, antithrombotic therapy in percutaneous coronary interventions, and disabling angina not amenable to revascularization procedures. Lifestyle interventions with diet and exercise in secondary prevention are also discussed. The last section is a structure-based perspective. As knowledge grows exponentially, the capability for clinical translation most often lags years behind resulting in important treatment gaps. On the other hand, a sound validation of new data is required before their large-scale application. The first chapter of this section is a thoughtful review of the evolving structures of coronary care units, current needs, and best utilization of available resources. The last chapters highlight the essentials of the most recent ACC/AHA and ESC guidelines recommendations written by the chairs of respective working groups. These organizations have realized the need to be proactive with the medical community to provide the best evidence-based medicine in a timely fashion to optimize rapid clinical translation. Thus, the working groups regularly evaluate the need for an update based on new data that are emerging, breaking the inertia usually found in such approach. A similar response is expected from the clinical community.

It is my hope you will enjoy the new edition of this text and that it will enrich your clinical practice and benefit for your patients.

Pierre Théroux, MD

LOOK FOR THESE OTHER TITLES IN THE BRAUNWALD'S HEART DISEASE FAMILY!

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Taylor: Atlas of Cardiac Computed Tomography
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Creager, Loscalzo and Dzau: Vascular Medicine
Moser and Riegel: Cardiac Nursing

SECTION I

Population-Based Perspectives

CHAPTER 1

The Past, the Present, the Future

Pierre Théroux

THE PAST: EMERGENCE OF A SYNDROME

The clinical description of a preinfarction syndrome closely followed that of angina almost 250 years ago, when Heberden[1] wrote the following:

> *There is a disorder of the breast marked with strong and peculiar symptoms and considerable for the kind of danger belonging to it.... The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called Angina pectoris. Those who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still, all this uneasiness vanishes. After it has continued some months, it will not cease so instantaneously upon standing still; and it will come on, not only when the persons are walking, but when they are lying down.*

The component of instability of angina was then recognized; it is now still how acute coronary syndrome (ACS) is most often recognized. In 1910, Sir William Osler formalized the description of frequent symptoms often preceding myocardial infarction,[2] setting the stage for 50 years of retrospective and prospective observations on manifestations, natural history, and discussions on definitions and potential causes. Wood,[3] in 1948, first attempted to halt the progression of the disease to death and myocardial infarction (MI). He reported the occurrence of MI or death in 12 of among 25 patients with an acute coronary insufficiency not treated with an anticoagulant and, in 3 of 33 patients given oral anticoagulants. It was suggested that the acute coronary insufficiency state is caused by a coronary circulation insufficient to meet the full demands of the myocardium at rest, yet sufficient to prevent MI.

A Florid Period

The modern era of coronary care was modeled through the 1960s to the mid-1990s. It started with external cardiac reanimation, universal acceptance of cardiac care units (CCUs), and electrocardiographic monitoring, and progressed to coronary angiography and coronary artery bypass grafting (CABG), reperfusion, antiischemic and antithrombotic therapy, and then to percutaneous interventions and stenting.

In parallel, the art of clinical trials grew to the levels of sophistication and performance we now know, and became standard to guide treatment and set the basis for evidence-based therapy. Early trials compared emerging medical management with no less than CABG. Drugs tested then include beta blockers, calcium antagonists, nitrates, and antithrombotic therapy—first with aspirin, then with heparin, and finally their combination. Research focused on pathophysiology, recognizing that unstable symptoms were caused by a rapid progression of the severity of the coronary obstruction causing a primary reduction in flow. Coronary artery

spasm as the main cause of this dynamic occlusion was rapidly ruled out, as coronary angiography performed during the very acute phase of the disease documented that thrombotic occlusion was the most frequent finding.

Keys to subsequent progress were the motivation of national cardiology organizations to master coronary artery disease, a major killer, and the strong commitment of many people, independent groups, pharmaceutical and industrial partnerships, and research and education at the local, national, and international levels.

Guidelines and Recommendations

The first official guidelines for the diagnosis and management of unstable angina (acute coronary syndromes) were published in 1994.[4] They were the tenth of a series of clinical practice guidelines published by the U.S. Department of Health and Human Services under the auspices of the Agency for Health Care Policy and Research (AHCPR) and the National Heart, Lung, and Blood Institute (NHLBI). The working panel was chaired by Dr. Braunwald. These practice guidelines were specifically developed and written to educate practitioners about appropriate health care for specific clinical entities.

Unstable angina at the time was a well-defined syndrome, recognized as being responsible for a significant amount of disability and death, and termed *acute coronary syndromes* to cover the full spectrum of severity of the disease process and clinical manifestations, from unstable angina (UA) to non–ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden death. Risk stratification, then based on clinical history, clinical features at presentation, and electrocardiographic changes, became a turning point for patient management. The biomarkers cardiac troponin I and T came a little later.[5] Their high sensitivity and specificity to detect myocardial necrosis were soon recognized, along with their power for risk stratification and for identifying patients who most benefited from more aggressive antithrombotic therapy and from invasive procedures. Another important gain of troponins is to set the focus on culprit lesions, an elevation in troponin levels being seen as diagnosis of a micro zone of myocardial cell necrosis caused by distal embolization of thrombotic material shed from a thrombus on an activated ruptured plaque. Assessment of troponin levels was assigned a grade 1a priority by the first sets of official guidelines for the management of UA NSTEMI, produced independently by the European Society of Cardiology and the American College of Cardiology (ACC)/American Heart Association (AHA) in 2000. The counterpart of no troponin level elevation and a normal electrocardiogram (ECG) become a low-risk situation, with no need for aggressive and urgent intervention and printable for an outpatient evaluation.

Clinical Trials and Registries

Proof of concept in the development of new therapeutics is usually achieved through phase 2 investigation demonstrates that the underlying theory, concept, procedure, or drug has a potential to be exploitable in a useful manner for improving quality of care and/or to show the feasibility in human application of a new intervention or a new drug. Phase 3 investigations are more rigorous and seek unbiased and objective documentation that the intervention is really useful. Entry criteria and objectives need to be well predefined because they will establish the framework for future approval and use. Whether trial results are considered positive or negative is based on the analysis related to the primary objective(s); secondary objectives, nonpredefined analyses, or substudies usually also raise new hypotheses of major interest that can generate new research. Strong recommendations in practice guidelines are based on phase 3 trial results. When lacking, weaker recommendations based on lower levels of evidence are usually made.

Statistics and epidemiologic data on cardiovascular diseases, as for other diseases, are obtained from various sources. Incidence and prevalence data are best obtained from government statistics. Registry data provide a broader perspective on the characteristics of selected populations of interest that are more like those in the real world. In clinical trials, populations are more dedicated, responding to specific inclusion and exclusion criteria. Registry data have been widely used in the last 2 decades as they reached an international scale. They produce valuable information about the pulse of the disease, including epidemiology, risk factors, and sociodemographic data in different environments and different lifestyles. Adding follow-up data to these registries provides estimates on natural history and effects of treatment, and adding serial cross-sectional samplings helps evaluate the changing pattern of the disease and the success of various interventions applied. Registries have now evolved as a means to monitor and improve quality of care and resource utilization. A drawback of these registries is that they become rapidly obsolete as feedback on performance is provided that stimulates autocorrection of deficiencies observed.

The first section of this textbook highlights data from four modern registries relevant to acute coronary syndromes, two from academic groups that studied risk factors and the natural history of the disease, and two from organizations that attempt to improve quality of care. Finally, a fifth mixed registry will be discussed for its positive impact on practice standards.

The INTERHEART Study (see Chapter 2) was a case-control study of close to 30,000. Cases were patients with a first MI recruited from 262 centers from 52 countries; controls were recruited from the surrounding community and matched for age and gender. Nine simple risk factors could account for more than 95% of the attributable risk for MI; the observations held true across all regions, ethnic groups, genders, and ages. While demystifying the causes of acute coronary syndromes, the findings of mental stress, all forms of tobacco, obesity (best defined by abdominal obesity and waist-to-hip ratio), nonfasting apolipoprotein B (apo B)–to–apolipoprotein A1 (apo A1) ratio, and simple measures of dietary pattern as production factors.

The REACH registry (see Chapter 3) enrolled almost 70,000 patients from 44 countries. The goal was to look at the pattern of risk factors associated with atherothrombotic disease across various vascular beds (coronary artery disease [CAD], cardiovascular disease [CVD], and peripheral vascular disease [PVD]) in geographically and ethnically diverse populations, and at their impact on prognosis and treatment modalities. The registry showed considerable gaps between risk-reducing recommended measures and current practice. As for INTERHEART, traditional cardiovascular risk factors accounted for most of the risk of the disease. The current obesity epidemic plaguing the industrialized nations of the world, particularly North America, and threatening emerging countries was underlined as a major cause of disease on a global scale. Short-term ischemic events were relatively high in the registry, the more so in individuals with more than one-vessel bed disease. An interestingly observation for all clinicians is that the disease, in general, is more malignant in symptomatic patients than in asymptomatic patients.

The Euro Heart Survey program was launched by the European Society of Cardiology (see Chapter 4) to assess variations in management and treatment of cardiovascular disease across Europe, particularly with regard to diagnostic procedures and treatments. The first survey, launched in 2000, involved more than 10,000 patients and was mainly descriptive of diagnoses and subdiagnoses, investigative means, and treatment applied in-hospital and at discharge. The second survey, in 2004, enrolled 6385 patients and

showed similar results but greater use of coronary angiography, percutaneous interventions (PCIs), and stents, mainly in ST-elevation ACS. An improvement in outcome was also observed that was to better adherence to guideline recommendations. Based on these observations and also on the wide variations in guideline adherence across different countries and in different centers within the same country, the Euro Heart Survey has moved from cyclic to continuous data collection in the ongoing ACS registry.

The U.S. counterparts of the Euro Heart Survey included the National Registry of Myocardial Infarction (NRMI), Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC and AHA Guidelines (CRUSADE), and Get With The Guidelines (GWTG) programs. In addition to providing a large national database to collect information on patients with ACS, these registries act as benchmarking tools to compare performance of various hospitals and adherence to guideline-recommended therapies. To improve quality of care further, the NCDR (National Cardiovascular Data Registry)-ACTION was created in 2007 by combining the NRMI and CRUSADE registries (see Chapter 5). The ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry is the largest, most comprehensive national ACS database and quality improvement initiative developed in the United States, enabling hospitals to measure their performance against national benchmarks. With more than 60,000 patient records and 350 participating hospitals, the main objective of the ACTION registry is to assess and report treatment patterns and outcomes of STEMI and NSTEMI in the United States. ACTION also merged with the AHA's GWTG program in 2009, forming ACTION-GWTG registry.

The GRACE registry, launched in 1999, recruited patients up to December 2007, it was supported by an unrestricted grant from Sanofi Aventis. More than 100,000 patients were recruited in up to 247 hospitals from 30 countries, from Europe, North and South America, and Australia and New Zealand. The first 10 to 20 patients qualifying for ACS symptoms plus other evidence of CAD were recruited monthly in each center. Data collection included admission and discharge diagnoses, clinical characteristics, treatment applied, with special attention to reperfusion therapy, in-hospital events, including bleeding events, and follow-up data for 6 months.[6] Participating physicians received confidential quarterly reports showing patient outcomes side by side with aggregate outcomes of all participating hospitals, allowing disparities between centers and regions to be characterized. Some of the contributions of GRACE were temporal trends in the rates and prognoses of ACS subdiagnostic categories,[7] patterns of drugs used, complications of anticoagulants and antiplatelet therapy, impact of prior aspirin, statin, atrial fibrillation, and congestive heart failure on outcome, influence of stenting and glycoprotein (GP) IIb/IIIa on survival, 6-month outcomes, predictors of readmission, death and MI, and the GRACE score.

THE PRESENT: A WELL-DEFINED ENTITY

Diagnosis

The diagnosis of ACS is first based on the recognition of typical or suggestive symptoms; signs at the physical examination are only scanty unless complications supervene such as congestive heart failure, mitral regurgitation, or others. Various phenotypes are recognized on a common pathophysiology. A 12-lead electrocardiogram (ECG) is first obtained and repeated as needed for evolving symptoms to ruleout STEMI, which would mandate consideration of immediate reperfusion therapy. The absence of ST-T changes in the presence of pain or other symptoms still does not rule out an electrically silent ACS. Alternative diagnostic methods are then needed, starting with recording the dorsal leads V7, V8, and V9 and, as needed, pursuing with imaging methods to detect ischemia, while alternative diagnoses are considered. 2D-echocardiography is readily available in the emergency department and is highly sensitive to detect regional dysfunction; however, it cannot differentiate an old infarct from acute ischemia (see Chapter 14). Other useful methods are a radionuclide perfusion scan, a CT scan, or a nuclear magnetic resonance study (see Chapter 15). The differential diagnoses of acute MI include aortic dissection, pulmonary embolism, pericarditis and eventually a pneumothorax, an esophageal problem, or one of many other potential causes.

Typically, high-risk patients require immediate coronary catheterization. Less acute patients at low to intermediate risk are investigated with serial ECG, cardiac troponins, and, as needed, echocardiography and/or radionuclide perfusion imaging. In patients with chest pain but no clear evidence of a high-risk ACS whose symptoms may also be attributed to an acute life-threatening pathologic condition of the aorta or pulmonary arteries, a "triple rule-out" (TRO) 64-slice CT angiography scan may be the most appropriate diagnostic test.[8] With this approach, a single scan incorporating the aortic arch down through the heart but not including the entire chest to limit radiation exposure, may eliminate the need for further diagnostic testing in over 75% of patients.

The timing of chest pain and its duration are important helps for the physician. Although ST resolution is generally accepted as the more practical marker for the success or failure of reperfusion therapy, chest pain that persists despite reperfusion therapy may suggest no effective reopening of the culprit lesion or no-reflow at the cellular level. Urgent angiography then needs to be considered. Chest pain that lasts more than 20 minutes is usually associated with an elevation of cardiac troponins. The third generation of cardiac troponin assays allows the detection of an elevation as early as 3 to 6 hours after the onset of pain, and enhances the sensitivity for the detection of very small microinfarcts. Further improvement is expected from the emerging sensitive troponin assays now being introduced in routine practice.[9]

These assays will clearly increase the rates of detection of myocardial cell necrosis, and new care and diagnostic algorithms will be needed to avoid over diagnosing myocardial infarction. The new universal definition of myocardial infarction discussed in Chapter 12 is already a step in that direction. The ultimate gain with the ultrafast assays should be more refined risk stratification.

Incidence and Manifestations

Cardiovascular diseases claimed nearly 1 million deaths in North America in 2005 although this rate had decreased by a third in the preceding 10 years.[10] In parallel with this decrease in mortality, the rates of in-hospital death from myocardial infarction decreased by one third in the Worcester Heart Attack Study between 1975 and 2005, whereas hospital survival rates increased by 10%.[11] Of interest, there has been a shift in the phenotype profile of ACS during that period, and in the profile of risk factors.

Evolving Profile of NSTEMI and STEMI

Although they are manifestations of a similar disease, the profiles of NSTEMI and STEMI have diverged over the years with regard to occurrence, diagnostic methods, treatment, and prognosis. Thus, rates of STEMI decreased in the last 20 years, whereas those of NSTEMI have remained similar or increased. In the Worcester study,[11] the yearly incidence of STEMI decreased from 0.71% to 0.10% between 1975 and 1997, whereas that of NSTEMI increased from 0.02% to

0.13%. The NMRI registry conducted in U.S. hospitals reported an increase in NSTEMI from 14.2% to 59.1% and a reduction in STEMI between 1990 and 1997 among 1,950,561 patients with a diagnosis of ACS.[12] In practice, NSTEMI now accounts for more than 66% of ACS diagnosis, compared with 33% not long ago.

1

Reasons for this changing pattern are multiple and not all recognized. The new diagnostic tools with troponin at the forefront have an increased sensitivity and also specificity reducing-false positive diagnoses and favoring selective hospitalization of higher risk patients. The markers are less critical in STEMI since ST-segment elevation on the 12-lead ECG should prompt coronary angiography and angioplasty, hopefully before any rise in creative kinase isoenzyme MB (CK-MB) and cardiac troponin levels.

Other reasons that explain the shift in the relative rates of STEMI and NSTEMI include a better control of risk factors and of statins that reduced plaque vulnerability; the widespread use of aspirin, which decreases the thrombus load on plaques; and earlier medical consultation and treatment allowing prevention of a more severe ischemic event. A most important explanation could be an insidious shift in the pattern of risk factors, modifying the fundamentals of the disease.

Concomitantly, fibrinolysis was shown useful for STEMI but deleterious in NSTEMI, and health systems have evolved to provide facilities for timely primary percutaneous coronary intervention (PCI) in STEMI to further reduce mortality and the major complications of congestive heart failure and cardiogenic shock. This structure is now increasingly applied to all ACS. In-hospital mortality rates in the Worcester Study fell between 1994 and 2006 from 10.4% to 6.3% for all MIs, 11.5% to 8.0% for STEMI, and 7.1% to 5.2% for NSTEMI, for an odds ratio of 23%, 24%, and 22%, respectively (all $P < 0.0001$).[13] In the international GRACE registry risk-adjusted hospital deaths declined 18% for STEMI and 0.7% for STEMI between 1999 and 2006 which could be imputed to greater adherence to practice guidelines and more appropriate use of reperfusion therapy, antithrombotic and antiplatelet therapies, statins, beta blockers and angiotensin-convering enzyme (ACE) inhibitors.[6,7] The importance of adherence to guidelines was further stressed by the NMRI registry by showing 11% reduction in in-hospital mortality for STEMI and NSTEMI for each 10% better compliance to guidelines (Fig. 1-1).[12]

Of note, STEMI became more prevalent in younger patients and NSTEMI in older patients in the NRMI registry.[13] In parallel with this shift, mean age increased from 64.1 years to 66.4 years and the proportion of women increased from 32% to 37% during the 16-year observation period. There were fewer patients reporting prior angina, prior MI, and a family history of CAD, but more patients with hypertension, dyslipidemia, current smoking, heart failure, and prior revascularization, stroke, and diabetes. The last three were more prevalent in NSTEMI. The same shifts in risk-factor profile were also seen in patients enrolled in clinical trials. Similar findings were also present in a 56-cent registry in France designed to test the validity of the new universal definition of MI.[14] A total of 2151 consecutive patients were enrolled. STEMI patients were more often treated with a revascularization procedure than their NSTEMI counterparts (PCI:74% vs. 57%; $P < 0.05$), and received more aggressive secondary prevention therapies at discharge, which was not supported by the disease severity. Rehospitalization rates at 1 year were 38% for STEMI and 41% for NSTEMI, and 16% in each group were revascularized. In-hospital mortality was similar (4.6% and 4.%), and 1-year mortality was 9.0% in STEMI and 11.6% in NSTEMI. The independent correlates of in-hospital mortality were untreated dyslipidemia, advanced age, diabetes, and low blood pressure, and the strongest predictors of 1-year mortality were heart failure and age. The predictors were the same for STEMI and NSTEMI.

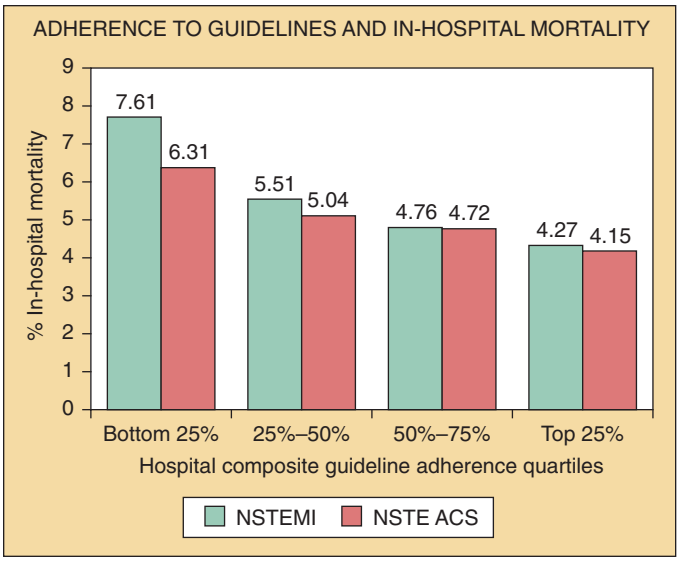

FIGURE 1–1 Pooling of data from 350 hospitals showing adjusted in-hospital mortality rates regrouped by quartiles of an index of adherence to guidelines. The data in *green* applies to NSTEMI and in *red* to all NSTEMI rates for overall patients with NSTE ACS for increasing quartile. All results were adjusted for age, sex, race, body mass index, patient insurance status, admission electrocardiograph (ST depression, transient ST elevation), admission cardiac marker status, presenting signs of heart failure, initial heart rate and systolic blood pressure, history of hypertension, diabetes mellitus, hypercholesterolemia, renal insufficiency, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, prior congestive heart failure, prior stroke, current/recent smoker, and family history of coronary disease. It can be concluded that in-hospital mortality is reduced by approximately 11% for each quartile better adherence to guidelines. *(From Peterson ED, Roe MTR, Mulgund J, et al: Association between hospital performance and outcomes among patients with acute coronary syndromes. JAMA 2006:295:1912-1920.)*

Clearly, the new risk-factor profiles of ACS are becoming the new the new challenges. They are very similar in STEMI and NSTEMI, but more extensive in NSTEMI resulting in more comorbidities.

THE FUTURE

Knowledge translation into clinical practice has become a priority. Indeed, the wide gap that existed not long ago between practice guidelines and actual practice has considerably narrowed due to educational efforts at various levels and timely updates of the recommendations. The European Society of Cardiology (ESC), ACC, and other organizations have implemented structures for monitoring practice and adherence to guidelines in various regions, hospitals, and medical practices providing a basis for eventual interventions (see Chapters 4 and 5).

Some of the pressing clinical needs in ACS are to develop better schemes for diagnosis and risk stratification, and for an individualized therapy. Because high-risk ACS is now recognized as an acute manifestation of atherothrombosis that mandates hospitalization and aggressive management-strategy treatment, the negative prognostic impact of the disease over the following months and years needs to be better addressed. Yet, our risk stratification schemes still mainly focus on markers of myocardial ischemia with the 12-lead ECG and cardiac troponins helped by 2-D echocardiography, radionuclide imaging, and provocative testing for ischemia. Time for an expanded perspective and a more

holistic approach to patient management that incorporate new biomarkers, new technologies, and innovative therapies has come. The purpose of this section is to present an insight into a few emerging biomarkers in blood constituents including the liquid phase and circulating cells, and the genome and proteome. Not covered are the unlimited new imaging technologies that can be coupled with various biologic markers including those derived from nanotechnology.

Blood Biomarkers

There exist numerous opportunities to identify the mechanisms of ACS; still there is a need to recognize among these mechanisms those which are prevalent in individual patients and that can become treatment targets. A panel of markers allows the monitoring of endothelial dysfunction and disruption, activation of platelet function and of the coagulation cascade, inflammation and immune and autoimmune reactions, cell necrosis, and many others. Assuming that high throughput and affordable technologies become available, mass analyses could be done on the large banks of frozen serum, plasma, and genetic material accumulated from clinical trials and registries.

This subsection is limited to the discussion of a few promising blood markers, B-type brain natriuretic factor (BNP and NT-proBNP), C-reactive protein (CRP), myeloperoxidase (MPO), and lipoprotein-associated phospholipase A2 (Lp-PLA2) that could help identify the patients at risk.

BNP and NT-proBNP. *These* cardiac neurohormones are released on ventricular stretching. The precursor pro-BNP is enzymatically cleaved into the N-terminal pro-BNP and then to BNP. These markers were first shown useful for the diagnosis and evaluation of heart failure. Subsequently, numerous prospective studies and analyses of large databases documented their powerful prognostic value to predict mortality in patients with stable and unstable CAD independently of conventional predictors. The assessment of BNP or NT-proBNP is a class 1B recommendation in the ESC (see Chapter 33) and a class 2B recommendation in the ACC/AHA guidelines (see Chapter 34) as an instrument to supplement assessment of global risk in patients with suspected ACS. In the GUSTO study, the 1-year mortality rates across a large cohort of ACS patients were 1.8%, 3.9%, 7.7%, and 19.2% with increasing quartiles of NT-proBNP ($P< 0.001$); this predictive value was independent of clinical and laboratory signs of left ventricular dysfunction.[16]

This unique property of BNP and NT-proBNP to predict mortality was reproduced in many studies. The brain natriuretic peptides also help discriminate the 2% to 4% of patients with suspect ACS who will develop an ischemic outcome despite a normal ECG and normal cardiac troponin values. Thus, NT-proBNP was measured at hospital admission in two independent registries, one from Germany composed of 1131 patients with ACS, the other from Argentina that included 1483 patients with chest pain. The latter served as a derivation cohort, and the former as the validation cohort. Among the 1178 troponin T (TnT)–negative patients, the receiver-operating characteristics curve analysis yielded an optimal cutoff value of 474 pg/mL to discriminate patients at higher risk. Higher values were associated with a higher risk for death in the two registries with adjusted hazard ratios (HR) of 9.56 (95% confidence interval [CI] 2.42 to 37.7, $P = 0.001$) and 5.02 (CI 2.04 to 12.33, $P < 0.001$), respectively.[17]

Inflammation Markers and CRP. None of the numerous inflammation markers studied to date in ACS could be validated as a therapeutic target (see Chapter 25). Although a nonspecific marker, CRP was shown useful to predict an adverse outcome. It was also suggested that the marker could contribute to the disease process, but the data in that direction remain controversial. CRPs half-life is 19 hours so that blood levels are mainly determined by the rate of production. The levels are very high in inflammatory and infectious diseases. They are also high in STEMI, rising within 6 to 12 hours after the onset of pain to peak within 48 hours. Elevated levels can be found at admission in NSTEMI when it has been preceded by unstable angina, suggesting that the disease process had been ongoing.[18] Elevated levels during the acute phase correlate in general with peak elevation of CK-MB, activated complement proteins and lower ejection fraction.[19]

Early elevation or persistent elevation past the acute phase lasting a few days is found in 40% to 50% of patients and is predictive of a higher rate of cardiac events, including death, MI, or recurrent ischemia at 12 months and death at 3 years.[20] In the CAPTURE trial, early death or recurrent MI at 72 hours was predicted by troponin levels but not by those of CRP; by contrast, CRP levels greater than 10 mg/L predicted late events at 6 months (18.9% vs. 9.5%) independently of troponin levels.[21]

The PROVE-IT TIMI 22 study randomized 3745 patients within 1 month after an ACS to high-dose of atorvastatin or moderate-dose of pravastatin.[22] Patients low-density lipoprotein (LDL) who achieved cholesterol levels less than 70 mg/dlL (1.8 mmol/L) had a reduced rate of recurrent myocardial infarction or coronary death during the 2-year follow-up than those who did not (2.7 vs. 4.0 events/100 person-years; $P = 0.008$), as well as patients who achieved CRP levels less than 2 mg/L (2.8 vs. 3.9 events/100 person-years; $P = 0.006$). The lowest rate of recurrent events (1.9/100 person-years) was achieved in patients with LDL cholesterol levels less than 70 mg/dL and CRP levels less than 1 mg/L. These results in post ACS patients are convincing as they are very much similar to those recently found in the prospective JUPITER trial which evaluated rosuvastatin versus placebo in primary prevention among individuals with LDL-cholesterol levels less than 130 mg/dL (3.4 mmol/L) but CRP levels greater than 2.0 mg/L.[23]

Other markers can also predict prognosis, particularly interleukin-6 which promotes the formation of CRP by the liver. A composite of markers can at times provide additional information because redundancy exists between the different inflammation pathways. One marker can add additive value, and the weight of different markers varies between patients. Figure 1-2 illustrates an example of the usefulness of multiple markers.[24]

Myeloperoxidase. MPO is a lysosomal protein abundantly present in neutrophils. It produces hypochlorous acid from hydrogen peroxide (H_2O_2) to destroy bacteria. MPO deficiency predisposes to immune deficiency. Antibodies against MPO have been implicated in various types of vasculitis. In one study of 604 sequential patients presenting to the emergency department with chest pain, initial plasma MPO levels predicted the risk of MI, need for revascularization, or death within 30 days and 6 months after presentation ($P < .001$) even in patients without evidence of myocardial necrosis defined by negative TnT values.[25] It was suggested that a single initial measurement of plasma MPO could independently predict the risk of major adverse events in the ensuing 6 months independently of the presence of myocardial necrosis. In a French-Canadian study, allele A of the MPO gene was less frequent in patients with CAD; the odds ratio for having documented CAD with the AA genotype was 0.138 (95% CI, 0.040 to 0.474), and with the AG genotype it was 0.639 (95% CI, 0.436 to 0.937) compared with the GG genotype.[26] Myeloperoxidase is an interesting marker that needs further validation studies.

Lipoprotein-associated Phospholipase A2. The interest in Lp-PLA2 has been renewed by observations on its role in culprit lesions and by the availability of orally active

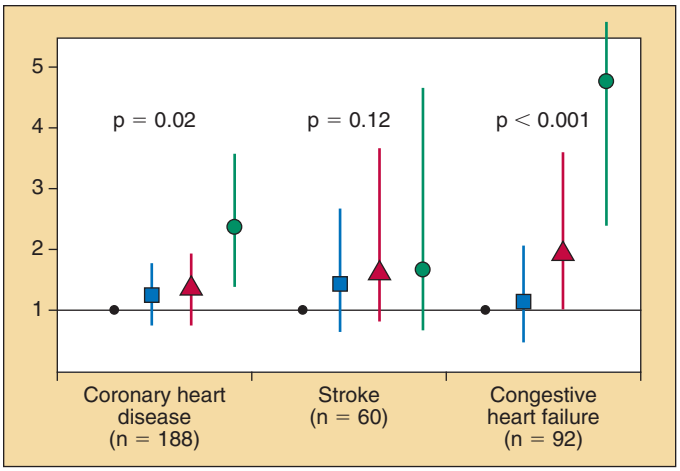

FIGURE 1–2 Results from a cohort of 2225 participants 70 to 79 years old without baseline CVD enrolled in the Health, Aging, and Body Composition study. Shown are the relative risk of an incident coronary heart disease, stroke, and congestive heart failure events detected during an average follow-up of 3.6 years by the number of inflammatory markers (IL-6, CRP, and TNF-α) in the highest tertiles (adjusted for age, gender, race, smoking, diabetes, hypertension, chronic obstructive pulmonary disease, body mass index, and HDL cholesterol, triglyceride, creatinine, and albumin levels). Symbols indicate RR; lines indicate 95% CI. *Black* represents the reference group with no elevated marker; *blue* is one marker in the highest tertile, *red* is two markers, and *green* three markers. While illustrating the importance of inflammation in the disease, the data illustrate the complexity of mechanisms implicated and the need for multiple approaches for the evaluation and the need. *(From Cesari M, Penninx BW, Newman AB, Kritchevsky SB, et al: Inflammatory markers and onset of cardiovascular events: Results from the Health ABC study. Circulation 2003;108:2317-2322.)*

inhibitors that are now tested in large clinical trials. Lp-PLA2 is produced by activated inflammatory cells (e.g., monocyte-derived macrophages, T cells, mast cells), carried in the circulation bound to lipoprotein B on low-density lipoprotein, and delivered in this form to monocytes and macrophages in lesion-prone segments of the arterial wall. Subsequent LDL oxidation leads to the formation of truncated phospholipids that can be hydrolyzed by Lp-PLA2. The process generates two bioactive lipid mediators, lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (NEFAs), which promote homing of inflammatory cells into active lesions and local accumulation of inflammatory mediators that further increase the expression of Lp-PLA2 (Fig. 1-3).[27] These mediators are cytotoxic to macrophages, facilitating their apoptosis and formation of a necrotic core in plaques. A histopathologic and immunolocalization in 25 sudden coronary death patients showed absent or minimal Lp-PLA2 staining in early plaques, but overexpression in thin-cap atheroromas and ruptured plaques in necrotic cores and surrounding macrophage and in apoptotic cells in regions of high macrophages density.[28]

Epidemiologic studies on primary and secondary prevention have reported positive associations between circulating mass and activity levels of Lp-PLA2 and the risk of cardiovascular disease (Fig. 1-4).[29] Alarger systematic meta-analysis of data from approximately 15,000 individual participants from all relevant observational studies is currently underway by the Lp-PLA2 Studies Collaboration and will soon be published.[30]

By contrast, measures of Lp-PLA2 activity obtained at admission for an ACS in the PROVE-IT study had no

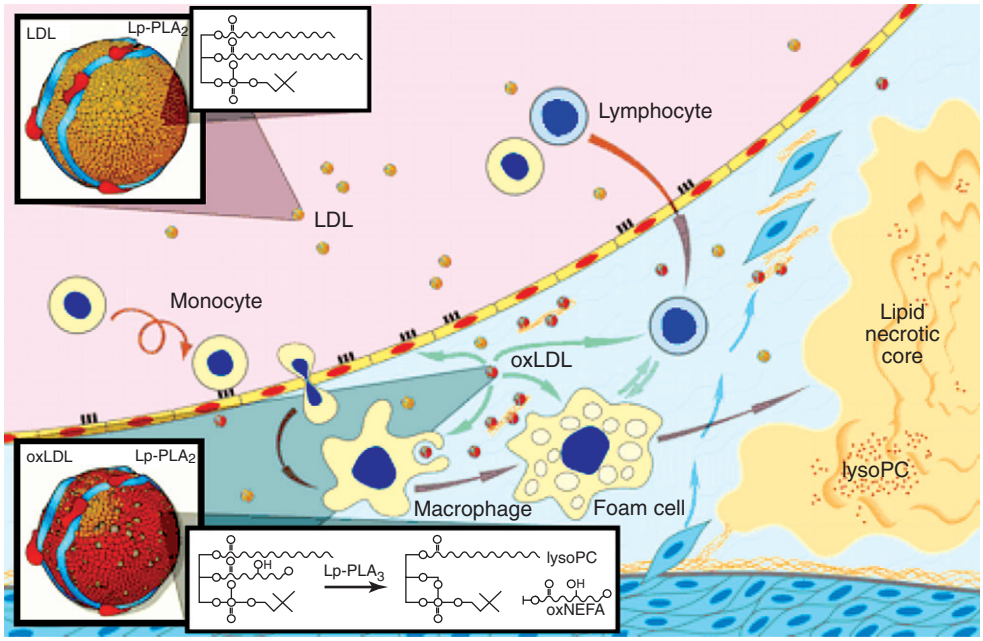

FIGURE 1–3 Schematic representation of the proposed proatherogenic mechanism of Lp-PLA2 in the vessel wall. Lp-PLA2 binds to apo B on LDL, its primary carrier, which delivers Lp-PLA2 to lesion-prone segments of the arterial wall. Subsequent LDL oxidation leads to the formation of truncated phospholipid in the sn-2 position, which is susceptible to enzymatic hydrolysis by Lp-PLA2. This results in the generation of two bioactive lipid mediators, lysoPC and oxidized NEFAs (oxNEFA), proposed to play an important role in the homing of inflammatory cells into lesion-prone areas and local increases in inflammatory mediators. The influx of inflammatory cells that express Lp-PLA2 increases its concentration in the vessel wall. Bioactive lipid mediators generated by Lp-PLA2 are also cytotoxic to macrophages, which may facilitate the formation of a necrotic lipid core in advanced atherosclerotic lesions. *(From Zalewski A, Macphee C: Role of lipoprotein-associated phospholipase A2 in atherosclerosis: Biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005;25:923-931.)*

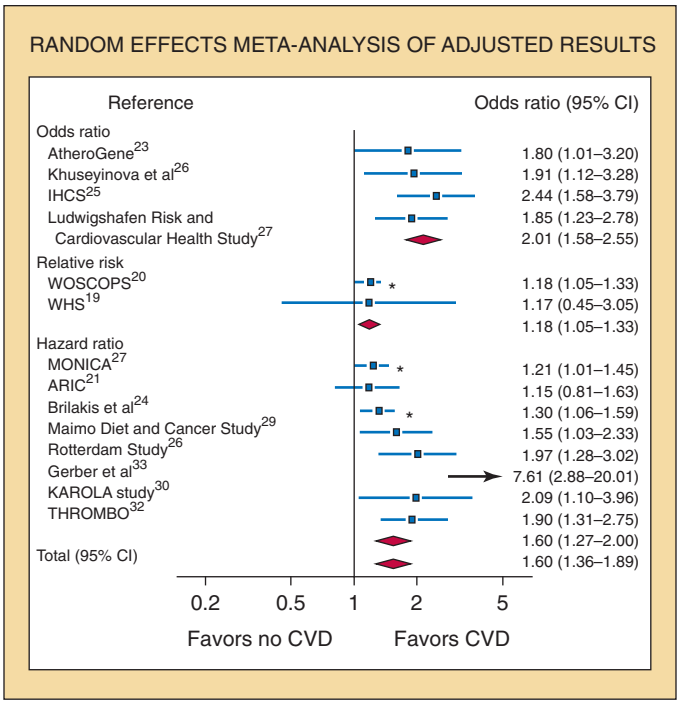

FIGURE 1–4 Random effects meta-analysis of adjusted results. The 14 studies reported a model adjusted for potential confounders. Shown here are the results for each study grouped by measure of association used in the original report. The overall pooled odds ratio of 1.60 is displayed as a *red diamonds*, with the width representing the 95% CI. The *asterisk* indicates studies with a cutoff of 1 standard deviation (SD); all others used extreme quantiles. ARIC, Atherosclerosis Risk in Communities; CVD, cardiovascular disease; IHCS, Intermountain Heart Collaborative Study; MONICA, MONItoring of trends and determinants in CArdiovascular disease; THROMBO, Thrombogenic Factors and Recurrent Coronary Events; WBC, white blood cell count; WHS, Women's Health Study; WOSCOPS, West of Scotland Coronary Prevention Study. *(From Garza CA, Montori VM, McConnell JP, et al: Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: A systematic review. Mayo Clin Proc 2007;82:159-165.)*

prognostic values for the occurrence of death, recurrent MI, revascularization, or stroke at 24 months. When obtained after 30 days in the same population, Lp-PLA2 activity, however, was a strong predictor of these events independently of cardiac risk factors, LDL, and CRP levels.[31] The lack of predictive value of admission levels can be explained by the decline in the acute phase in blood levels of LDL cholesterol, and therefore of Lp-PLA2 transport capacity. Altogether, these observations suggest that the measure of Lp-PLA2 is not useful during the acute phase, unlike cardiac markers, but when done later is predictive of inflammation within the plaque and of subsequent high risk of a recurrent ischemic event.

Thus, the inhibition of Lp-PLA2 in diabetic and hypercholesterolemic swine with advanced coronary atherosclerosis inhibits plasma and lesion Lp-PLA2 activity and lysoPC content to decrease the necrotic core within the plaque while promoting expression of an anti-inflammatory gene associated with macrophage and T-lymphocyte functioning.[32] The human counterpart can be found in a double-blind placebo-controlled study using intravascular ultrasound (IVUS)-based imaging, which suggested a benefit of darapladib, an orally active inhibitor.[33] The drug, or placebo, was administered for 1 year to 330 patients with angiographically documented CAD. At 12-month follow-up, there were no differences between the two groups in levels of LDL cholesterol, but there was a significant 59% decrease in Lp-PLA2 activity with darapladib. No effects could be detected on the primary end points of plaque deformability measured by IVUS palpography and plasma levels of CRP. Lp-PLA2, however, inhibited by 50% the necrotic core volume (-0.514 mm^3 vs. +4.518 mm^3 with placebo), resulting in a significance of 5.032 mm^3 ($P = .01$). These intraplaque compositional changes occurred without a significant treatment difference in total atheroma volume.

Gene-based Research

Impressive progress has been made in our understanding of the genome and proteome, but much further research is needed for widespread clinical translation of our knowledge. Most promising for the future is a thorough understanding of the clinical information provided by the genome, proteome, transcriptome, and metabolome, and the integration of all these sciences.

The genome contains all the hereditary information encoded in human DNA, both in genes and noncoding sequences organized into chromosomes that release the genetic codes to be transcribed. These are carried by messenger RNA (mRNA) to the ribosome where new proteins are synthesized. The set of all RNA molecules, or transcripts, produced in one cell or a population of cells is termed the transcriptome; it reflects the genes actively expressed at any given time under the influence of external environment conditions. The proteome is the entire set of proteins expressed by a genome, cell, tissue, or organism at a given time under defined conditions. The circulating blood is particularly rich in the aforementioned as it is in a constant dynamic exchange with the various tissues and organs, and can be the source of countless information about health and disease. The metabolome represents the unique chemical fingerprints that specific cellular processes leave behind, representing a collection of all end-products and metabolites of gene expression.

Cell Markers

Circulating blood cells include red and white cells and platelets. The simple blood count is part of routine blood work and is already informative about a variety of pathologic states. Cell typing is required for blood transfusions and organ transplantation, and for cell therapy. New investigative means and technologies are in constant development. Most promising for the near future is the characterization of membrane lipid rafts (Fig. 1-5)[32] and of circulating microparticles (Fig. 1-6).

Lipid rafts are glycosphingolipid and cholesterol-enriched microdomains found in cell membranes that contain signaling molecules such as heterotrimeric G proteins and numerous receptor types, particularly the G protein–coupled receptors (GPCRs), also known as seven-transmembrane domain receptors.[33] The GPCRs constitute a large and diverse family of proteins that sense molecules outside the cell and activate signal transduction pathways inside the cell and, ultimately, cellular responses. They are among the largest and most diverse protein families in mammalian genomes. Lipid rafts are sensitive to ligand stimulation and their state of activation or dimerization and permit their clustering and partitioning in and out of the rafts. Thus, it was demonstrated that purinergic G protein–coupled P2Y 12 receptors (P2Y12) preferentially associate as functional oligomeric complexes within microdomains at the cell surface and that the active metabolite of clopidogrel bridge to the P2Y12, resulting in oligomers dissociating into dimeric receptors partitioned out of lipid rafts, which then lose the ability to bind their endogenous ligands.[34]

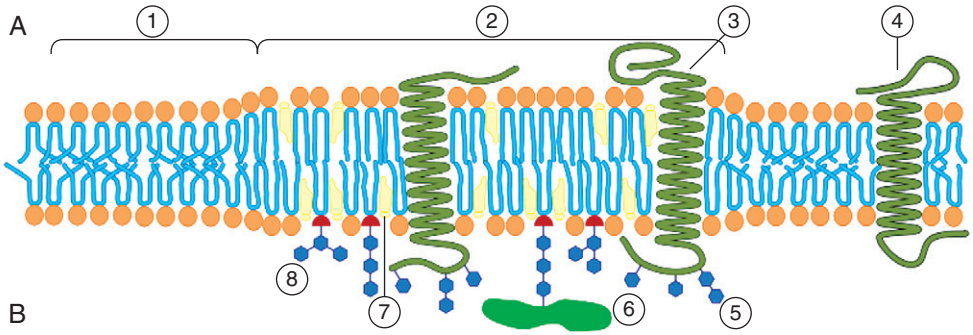

FIGURE 1–5 Schematic representation of lipid raft structures in a plasma membrane. The dynamic clustering of sphingolipids and cholesterol form a specialized part of the membrane known as lipid rafts, which float within the fluid bilayer. They constitute distinct signaling platforms dependent on lipid raft subtype and composition. They serve as platforms for the attachment of proteins when membranes are moved around inside the cell and during signal transduction. Lipid rafts can merge, favoring interactions among constituent proteins. **A,** Intracellular space or cytosol. **B,** Extracellular space or vesicle or Golgi apparatus lumen. 1, Nonraft membrane. 2, Lipid raft. 3, Lipid raft–associated transmembrane protein. 4, Nonraft membrane protein. 5, Glycosylation modifications (on glycoproteins and glycolipids). 6, GPI-anchored protein. 7, Cholesterol. 8, Glycolipid. *(From Fijałkowski AJ: Lipid raft organisation scheme, 2006. Available at: http://en.wikipedia.org/wiki/File:Lipid_raft_organisation_scheme.svg).*

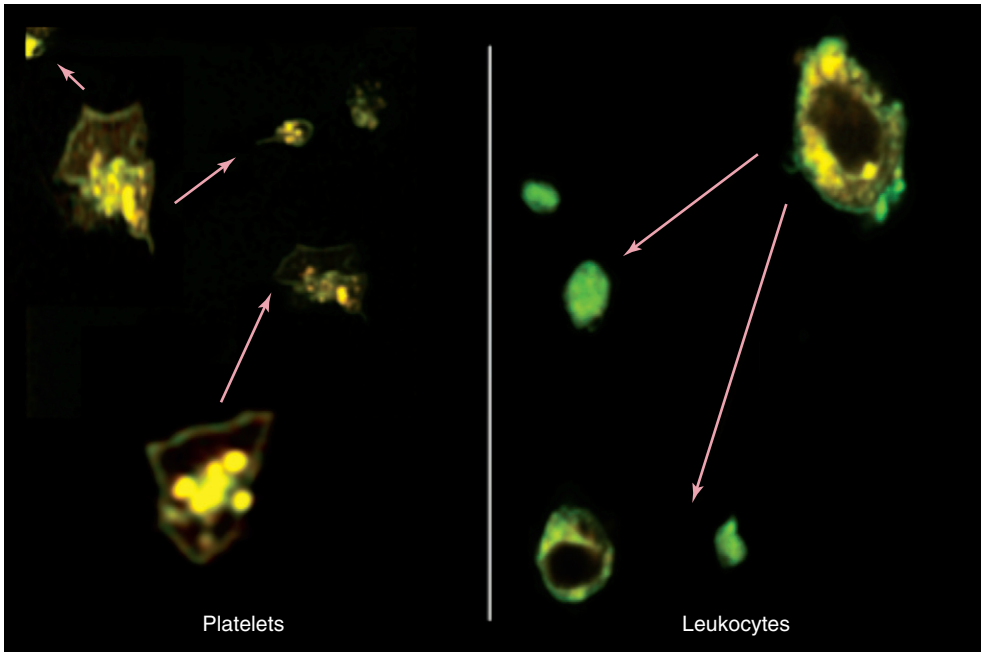

FIGURE 1–6 The arrows point to circulating microparticles identified by fluorescence microscopy in the atmosphere of platelets (*left*) and a leukocyte (*right*). These MPs are generated when cells are activated or apoptotic. They can disseminated systematically and carry the potential to exchange at a distance with other cells via homotypic and heterotypic interactions. Thus, these microparticles can be prothrombotic or proinflammatory.

Microparticles (MPs) are 50 to 100 nm in diameter and are shed in the atmosphere of activated or apoptotic cells, mainly platelets, leukocytes, endothelial cells, and smooth muscle cells (see Fig. 1-6). They contain a small part of a plasma membrane surrounding a small amount of cytosol. MPs can be sampled in the blood and characterized with regard to cell of origin by membrane antigens and to activity by their bioactive effectors. They are indicators of cell dysfunction and of a thrombotic and inflammatory state. Furthermore, these MPs are disseminated systematically via homotypic and heterotypic cell interactions with the potential of carrying the disease process at a distance to other tissues or organs. Thus, monocyte-derived MPs transport tissue factor and can trigger intravascular thrombus formation and platelet-derived MPs are thrombotic by exposing the phosphatidylserine membrane surface, which facilitates the assembly of coagulation factors.

Redefining Risk and Therapy

Of academic interest are the results of an epidemiologic cohort study from Malmö, Sweden,[35] that enrolled 5067 participants (mean age, 58 years; 60% women), with no cardiovascular disease at entry, between 1991 and 1994 and followed until 2006 (Table 1-1). The goal was to identify markers that could help predict a first cardiovascular event beyond conventional predictors. In backward-elimination models, the strongest predictor markers for a first CV event were CRP, cystatin C, and NT–pro-BNP and, for a first coronary event, cystatin C and NT–pro-BNP. One important current challenge is to tailor risk stratification and treatment to the evolving patterns of risk factors, which are largely metabolic. Whereas classic markers have focused on markers of cell necrosis for early risk stratification and treatment titration, the new risk stratification measures also include patient characteristics and comorbidities, mainly diabetes, the metabolic syndrome, and chronic kidney disease to extend risk prediction into follow-up.

Diabetes

As many as 20% to 30% of patients currently admitted for ACS suffer diabetes mellitus (DM), a major risk factor and an important predictor of impaired prognosis in STEMI and NSTEMI. In a combined analysis of the GUSTO-I, GUSTO-III, and GUSTO-V trials, diabetic patients with STEMI compared with nondiabetic patients had a greater risk of in-hospital mortality (9.5% vs. 5.5%; $P < .001$) and 30-day mortality (10.4% vs. 6.0%; $P < .001$).[36] In the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry, which involved patients with UA-NSTEMI, diabetes was an independent predictor of 2-year mortality (18% vs. 10% in nondiabetics; relative risk [RR], 1.57; 95% CI, 1.38 to 1.81; $P < .001$].[37] In a retrospective analysis of a prospective cohort of 2499 consecutive patients admitted to 11 British hospitals for confirmed ACS, all-cause mortality during a median 2-year follow-up was 45% higher in diabetics. However, some heterogeneity exists in the prognosis of diabetics in the cohort. Without a history of CVD, the mortality rates were similar with and without DM (18.8% and 19.7%, respectively); with a history of CVD, mortality was higher in diabetics (46.7% and 33.2%; $P < .001$) and troponin I levels were higher ($P < .001$).[38]

Clearly, diabetic patients with an ACS will profit from a more aggressive management strategy combining drugs and interventions. A meta-analysis of six randomized trials of GP IIb/IIIa inhibitors, involving 658 diabetic patients with UA-NSTEMI, has shown a significant reduction in 30-day mortality with GP IIb/IIIa inhibition (from 6.2% to 4.6%; OR, 0.74; 95% CI, 0.59 to 0.92; $P = .007$). In this analysis, the interaction between platelet GP IIb/IIIa inhibition and diabetic status was statistically significant ($P = .036$).[39] The TRITON trial compared prasugrel with clopidogrel in 13,608 randomized PCI-eligible patients with STEMI, unstable angina, or NSTEMI, of whom 3146 were diabetics.[40] CV death or nonfatal MI or stroke occurred in 9.9% of the 10,462 patients without diabetes, in 13.4% of the 2370 diabetics not on insulin, and in 18.3% of the 776 insulin-treated diabetics (P for trend < .0001). The benefit was greater with prasugrel than with clopidogrel in these patients (12.2% vs. 17.0%; hazard ratio [HR], 0.70; 95% CI, 0.58 to 0.85; $P < .001$) than among the 10,462 patients without diabetes (9.2% vs. 10.6%; HR, 0.86; 95% CI, 0.76 to 0.98; $P = .02$). The adjusted HR for prasugrel versus clopidogrel was 0.74 for diabetics not on insulin and 0.63 for diabetics on insulin ($P = .009$ for both subgroups). This protection with prasugrel was obtained without excess bleeding risk, illustrating that when appropriately used in thrombotic states, the benefit of antiplatelet and anticoagulant therapy usually far exceeds the bleeding risk.

Although no randomized studies formally compared an early invasive versus conservative strategy in diabetic patients with NSTEMI, subgroup analyses of large-scale randomized studies have suggested a strong positive impact of the early invasive strategy. In the FRISC II study 2457 patients with UA-NSTEMI were randomized to an invasive or conservative strategy; a significant 22% reduction in death or MI at 6 months was seen with the invasive strategy. The relative risk reduction (RRR) was the same in nondiabetic and diabetic patients but the absolute gain was greater in diabetic patients (6.2% vs. 2.3%) because of higher event rates in this group. At 1 year, diabetic patients undergoing early invasive therapy had a 38% risk reduction in death rates (7.7% vs. 12.5%, not significant).[41] The TACTICS trial applied an invasive strategy within 48 hours of admission and reported a significant 22% reduction in the relative risk of death, MI, or rehospitalization for ACS at 6 months compared with the early conservative strategy for 2220 patients, all being treated with aspirin, clopidogrel, and the GP IIb/IIIa receptor inhibitor tirofiban. Diabetic patients ($N = 6458$) derived a greater benefit than nondiabetics from an early invasive strategy, both in terms of absolute (7.6% vs. 1.8%) and relative 6-month event reduction (27% vs. 13%).[42] The reduction of the 1-year death or MI rates was more important in patients with diabetes ($N = 299$)

TABLE 1–1 Novel and Conventional Biomarkers for Prediction of a First Cardiovascular Event

Biomarker	Hazard Ratio	P
First Cardiovascular Events		
CRP	1.19	.002
Cystatin C	1.13	.006
MR–pro-ADM	1.12	.04
MR–pro-ANP	1.12	.04
NT–pro-BNP	1.22	<.001
First Coronary Events		
Cystatin C	1.15	.006
MR–pro-ADM	1.21	.002
NT–pro-BNP	1.28	<.001

Data from a prospective cohort analysis based on biomarkers shown predictive of first CV events ($N = 4483$ [364 events]) and first coronary events ($N = 4600$ [216 events]). These have been adjusted for age, gender, antihypertensive treatment, systolic and diastolic blood pressure, body mass index, diabetes, levels of LDL and HDL cholesterol, and current smoking.

MR–pro-ADM, midregional proadrenomedullin; MR–pro-ANP, midregional atrial natriuretic peptide.

Data from Melander O, Newton-Cheh C, Almgren P, et al: Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA 2009;302:49-57.

in terms of RRR (39%) and absolute risk reduction (ARR; 9.3) compared with nondiabetics (RRR, 28%; ARR, 3.1%).

Metabolic Syndrome

The risk factors and pathophysiology of the metabolic syndrome and type 2 diabetes share many similarities. Needless to say, the most important causative factor is excessive caloric intake, not matching metabolic factors. This translates into central obesity, low high-density lipoprotein (HDL) cholesterol, reduced tissue insulin sensitivity, and compensatory hyperinsulinemia and, as a result, hypertension, high levels of postprandial triglycerides, reduced HDL cholesterol, a subclinical inflammatory state, and a prethrombotic state.[43]

The proinflammatory state is manifested by an elevation of CRP induced by the release of inflammatory cytokines from the excess adipose tissue. Prospective studies in middle-aged individuals have noted that increased serum CRP levels may predict the development of metabolic syndrome.

The prothrombotic state includes endothelial dysfunction, hypercoagulability, hypofibrinolysis, and platelet activation. It is characterized by increased plasminogen activator inhibitor type 1 (PAI-1) and fibrinogen, which is also an acute-phase reactant, illustrating one of the many interactions existing between inflammation and thrombosis.

Table 1-2 provides the new definition of the metabolic syndrome as recently proposed by the International Diabetes Federation (IDF), NHLBI, World Heart Federation, International Atherosclerosis Society, and AHA.[44] Most have agreed that abdominal obesity should not be a prerequisite but one of the five proposed criteria. In this context, the presence of any three of five risk factors is required for the diagnosis of a metabolic syndrome. The definition of the metabolic syndrome does not make a consensus, because the American Diabetes Association has found the definition of some components ambiguous and has questioned the validity of the syndrome and the difference between treating the syndrome versus treating the individual components.[45]

TABLE 1–2 New Definition of the Metabolic Syndrome

Measure	Categoric Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is alternate indicator)	≥100 mg/dL

*It is recommended that the International Diabetes Federation (IDF) cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.

†The most commonly used drugs for elevated triglyceride and reduced HDL-C levels are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglyceride and low HDL-C levels. High-dose or ω-3 fatty acids presumes high triglyceride levels.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

From Iberti KG, Eckel RH, Grundy SM, et al: Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-1645.

The reported incidence of the syndrome in ACS patients varies between 29% and 46%, with the prevalence being higher in subjects younger than 45 years. In one controlled study that included 183 men with a mean age of 40.8 ± 3.5 years, a metabolic syndrome was present in 51.5% of those who developed an ACS compared with 26.0% of 200 matched controls (OR, 1.93; 95% CI, 1.13 to 3.28); the predictive value in this study was better performance than that of the Framingham score (OR, 0.98; 95% CI, 0.92 to 1.05).[46] The metabolic syndrome also affects prognosis negatively after an ACS has developed. Thus, in a study of 480 consecutive patients monitored for cardiovascular evaluation and management 3 months after an ACS, 5.3% of patients with a metabolic syndrome died within 16 months compared with 1.4% of patients without the syndrome ($P < .01$), despite optimal LDL-C and blood pressure control reached in the two groups.[47] In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial,[48] the primary end point event of death, nonfatal MI, cardiac arrest, or recurrent unstable myocardial ischemia occurred after 16 weeks in 19% of 1161 patients with the syndrome compared with 14% of 1877 patients without it (HR, 1.49 ; 95% CI, 1.24 to 1.79; $P < .0001$). In this study, the criteria that best predicted events were diabetes and low HDL. The RRR with patients given 80 mg atorvastatin daily compared with placebo was in the same range in patients with or without metabolic syndrome.

Chronic Kidney Disease

It is assumed that more than 20% of patients with ACS have at least moderate renal failure (creatinine clearance [CrCl], 60 mL/min) and almost 40% have some renal impairment (CrCl, 90 mL/min).[49] Chronic kidney disease (CKD) represents an important risk factor in ACS because it is associated with impaired in-hospital and long-term outcome. In a meta-analysis of four large clinical STEMI and UA-NSTEMI trials defining CKD by an arbitrary CrCl cutoff of less than 70 mL/min (Cockroft and Gault method), the hazard ratio for total mortality with CKD compared with no CKD in NSTEMI was 0.88 (95% CI, 0.83 to 0.95) at 30 days and 0.81 (95% CI, 0.70 to 0.92) at 180 days, with no differences between STEMI and NSTEMI. For the end point of death or MI at 180 days in NSTEMI, the hazard ratio was 0.93 (95% CI, 0.90 to 0.96).[52] Among 45,343 patients with UA-NSTEMI registered in the CRUSADE Quality Improvement Initiative, the 6560 patients with moderate to severe CKD were older, more often diabetic, more likely to present with signs of congestive heart failure, and less likely to be treated with medications, undergo invasive cardiac procedures, and be given discharge counseling. They had a 50% increased risk of mortality, and a 70% increased likelihood of blood transfusion (Table 1-3).[53] Less severe forms of CKD are also associated with significant cardiovascular risk, and community-based studies have documented an inverse relationship between renal function and adverse cardiovascular outcomes. This relationship consistently occurred at estimated glomerular filtration rates (eGFR) of 60 mL/min/1.73 m^2).[54]

Mechanisms for the cardiorenal syndrome are numerous. They include comorbidities already associated with the disease, such as diabetes, hypertension, left ventricular failure, and left ventricular hypertrophy. CKD in itself has an independent negative prognostic impact in addition to other risk factors. Causative factors include anemia, blood transfusions, myocardial micronecrosis, and high levels of fibrinogen, homocysteine, lipoprotein(a), oxidized LDL, and inflammatory mediators. Some markers that correlate with

TABLE 1–3 In-Hospital Cardiac Events in Patients with a Non–ST-Segment Elevation and Chronic Renal Disease

Outcomes	CKD, % (*N* = 6560)	Non-CKD, % (*N* = 38,783)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Death	9.0	3.6	2.62 (2.32-2.97)	1.54 (1.35-1.75)
Reinfarction	3.7	2.7	1.34 (1.17-1.53)	1.25 (1.10-1.43)
Death or reinfarction	11.6	5.8	2.08 (1.86-2.32)	1.45 (1.30-1.61)
Cardiogenic shock	4.5	2.3	1.93 (1.68-2.23)	1.37 (1.16-1.61)
Congestive heart failure	16.5	8.1	2.16 (1.97-2.36)	1.18 (1.09-1.29)
Transfusions	26.7	12.9	2.16 (2.02-2.31)	1.76 (1.65-1.88)

Data from 45,343 patients with NSTEMI acute coronary syndrome enrolled in the CRUSADE Quality Improvement Initiative comparing in-hospital event rates in patients with and without moderate to severe chronic kidney disease.

From Han JH, Chandra A, Mulgund J, et al: Chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. Am J Med 2006;119:248-254.

adverse cardiovascular outcomes are troponins, asymmetric dimethylarginine, PAI-1, homocysteine, natriuretic peptides, CRP, serum amyloid A protein, hemoglobin, and ischemia-modified albumin.[54]

A most important contributor to the severe prognosis in CKD patients is undertreatment. Indeed, beneficial therapies are paradoxically less likely to be administered as renal function declines. Of the 6518 consecutive patients with an ACS enrolled in Gulf Registry of Acute Coronary Events prospective registry, 2828 (43%) had mild chronic renal insufficiency (CRI) (eGRF, 60 to 89 mL/min), 1304 (20%) had moderate CRI (eGRF, 30 to 59 mL/min), and 345 (5%) had less than severe CRI (30 mL/min). CRI patients were older, had a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia. They had a higher resting heart rate at admission and frequently had atypical and delayed presentations. Compared with the normal estimated glomerular filtration group, CRI groups were less likely to receive antiplatelet drugs, beta blockers, ACE inhibitors, and statins and were less likely to undergo coronary angiography. In-hospital heart failure, cardiogenic shock, and major bleeding episodes were significantly higher in all CRI groups. In multivariate analysis, mild, moderate, and severe CRI were associated with a higher adjusted odds ratio for death of: 2.1 (95% CI, 1.2 to 3.7), 6.7 (95% CI, 3.9 to 11.5), and 12.0 (95% CI, 6.6 to 21.7) respectively.[55]

Potential reasons for this subtherapeutic performance include concerns for further worsening of renal function and/or therapy-related toxic effects caused by low clearance rates, despite the renal protection that can be afforded by avoidance of high contrast medium load, blood loss, and periprocedural hypotension. Moreover, only a few patients with advanced renal disease have been enrolled in ACS trials because of exclusion criteria or they were deemed to be too sick.

Noteworthy, in the 4634 patients with unstable angina or acute MI enrolled in Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial, catheterization with or without PCI compared with medical therapy during follow-up was not associated with significant differences in long-term glomerular filtration rate (GFR) ($P = .09$) in adjusted analyses of predictors of percentage change in GFR. As GFR declined, the proportion of subjects experiencing death versus a GFR reduced by 50% or end-stage renal disease (ESRD) qualitatively increased. In adjusted analyses, every 10 mL/min/1.73 m^2 decrease in GFR 90 was associated with a 15% increased hazard of death (HR, 1.15; $P = .01$). These data suggest that in CKD subjects, the risk of death outweighs the risk of reduced GFR or the development of ESRD following ACS, and that catheterization with or without PCI is not associated with significant differences in long-term renal function. The presence of CKD should not therefore preclude potentially beneficial invasive interventions, excluding only patients with a CrCl of 30 mL/min.[56]

Similarly, the benefit of revascularization in high-risk ACS may well exceed the risk associated with the procedure. The very large nationwide Swedish CCU registry enrolled between 2003 and 2006 a total of 23,262 NSTEMI ACS patients aged 80 years or younger to study how the estimated glomerular filtration rate influences the prognosis of patients treated with an invasive management revascularization within 14 days of admission versus medical therapy.[57] It was found by Cox regression model with adjustment for propensity score and discharge medication that fewer patients with declining renal function and the overall 1-year mortality was 36% lower (HR, 0.64; 95% CI, 0.56 to 0.73; $P < 0.001$) in patients undergoing an invasive strategy compared with those who did not. The lower mortality associated with early revascularization was not, however, uniformed across the five renal function stages (Fig. 1-7). The lower mortality observed with invasive therapy declined with lower renal function, with no difference in mortality in patients with kidney failure (eGFR, 15 mL/min/1.73 m^2) or in those receiving dialysis (HR 1.61, 95% CI, 0.84 to 3.09, $P < 0.15$).

Other confounding factors in CKD are the interpretation of troponin elevations (see Chapter 12) and the selection and titration of drugs, particularly the anticoagulants, because these patients are also at a higher risk of bleeding. In an analysis of 30,136 patients from the CRUSADE registry, excess bleeding occurred in 6.6% to 22.2% of patients in relation to the degree of excess doses of drugs and the number of agents administered; mortality and length of stay were also higher among those patients administered excessive dosing.[58]

In general, loading doses are the same in patients with or without CKD, but the maintenance dose should be carefully selected because excessive dosing is a frequent cause of bleeding. Although heparin may have slightly delayed clearance in kidney failure, this poses a negligible issue because its therapeutic effects are directly monitored. Low-molecular-weight heparins need to be carefully titrated to prevent bleeding and are generally contraindicated or dose-adjusted in patients with severe renal failure (CrCl < 30 mL/min). Bivalirudin needs no adjustment with CrCl greater than 30 mL/min; with a lower CrCl, the infusion dose is decreased to 1 mg/kg/hour. Fondaparinux is also renally excreted; in the OASIS-5 trial, however, it was safer at dosages of 2.5 mg once daily than enoxaparin for patients with severe renal failure, despite the use of reduced enoxaparin at dosages of 1 mg/kg once rather than twice daily.[59] The small-molecule GP IIb/IIIa inhibitors are dose-adjusted—tirofiban to a half-dose in patients with CrCl less than 30 mL/min and eptifibatide to a half-dose with CrCl less than 50 mL/min. Note that tirofiban is removed from the circulation by dialysis and that eptifibatide is almost completely excreted renally.

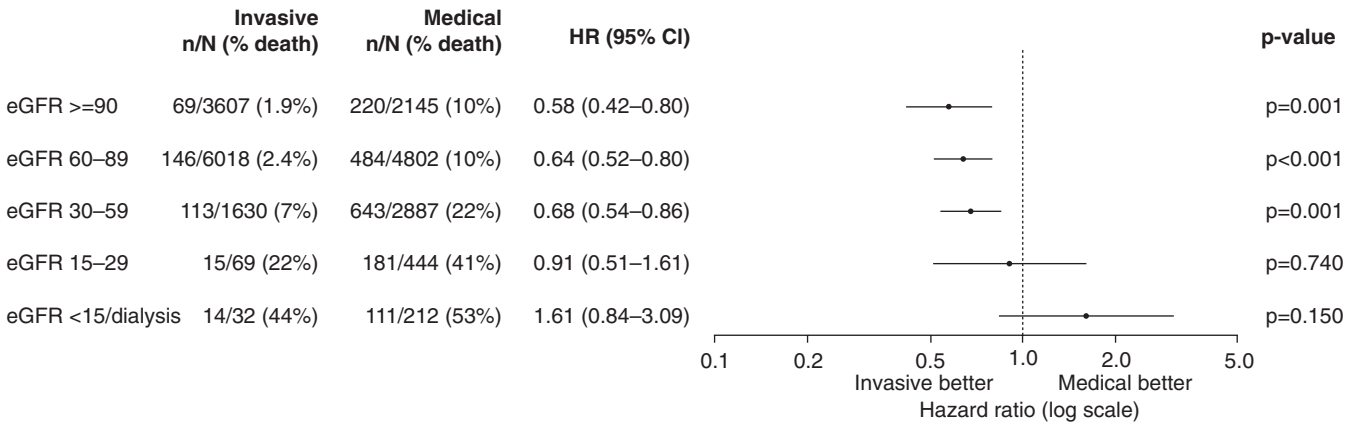

Figure 1-7 Influence of renal function on prognosis of patients with NSTEMI treated with revascularization within 14 days of admission versus medical therapy. Glomerular filtration rates (eGFR) were estimated with the Modification of Diet in Renal Disease Study formula calculated with creatinine, age, gender, and race. The National Kidney Foundation Kidney Disease outcomes Quality Initiative definition was used for renal function staging: eGFR ≥ 90 mL/min^{-1}/1.73 m^{-2} (normal), and eGRF 60 to 90 mL/min^{-1}/1.73 m^{-2} (mild), eGRF of 30 to 59 mL/min^{-1}/1.73 m^{-2} (moderate), 15 to 29 mL/min^{-1}/1.73 m^{-2} (severe), and 15 mL/min^{-1}/1.73 m^{-2} (renal failure) or receiving dialysis.

By a multivariable Cox regression model with adjustment for propensity score and discharge medication, patients treated with early revascularization had an overall improved survival at 1 year (HR, 0.64; 95% CI, 0.56 to 0.73, $P < 0.001$). The magnitude of the difference in mortality was similar in groups with normal to moderate renal function with a gradient toward less of a mortality difference with decreasing renal function; this was most pronounced with severe kidney failure (eGFR < 15 mL/min^{1}/1.73 m^{2}) or who were receiving dialysis where a trend to harm with invasive therapy. There was a significant interaction between revascularization and renal function group ($P < 0.001$), but no interaction between gender and revascularization. *(Data reproduced with permission from Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: Data from the Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Circulation 2009;120;851-858.)*

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CHAPTER 2

Risk Factors Predicting Nonfatal Myocardial Infarction: The INTERHEART Study

Clara K. Chow, Koon K. Teo, and Salim Yusuf

Globally, cerebrovascular disease (CVD), which includes coronary heart disease (CHD), strokes, and peripheral arterial diseases, is the leading cause of death and is a major disease burden.[1] Although age adjusted CVD death rates have declined in several Western countries in the last decades, CVD rates have markedly increased in low- and middle-income countries[2] and now approximately 80% of the burden occurs in these countries. Several factors contribute to the trend toward increasing rates of CVD in developing countries. First, decreasing mortality rates from acute infectious disease have resulted in increased life expectancy, which in turn leads to a higher proportion of individuals reaching middle and old age, ages at which they are at risk of atherothrombotic events. Second, lifestyle and socioeconomic changes associated with urbanization may lead to higher levels of risk factors for CVD.[3] Third, some populations or individuals (e.g., because of lifestyle or genes) may be particularly susceptible to the adverse effects of a particular environmental factor; for example, South Asians appear to develop diabetes more often than individuals of European descent, which may be the result of an inherent susceptibility or perhaps of unique diets, which include highly refined carbohydrates.

Current knowledge about CHD and CVD prevention is primarily derived from studies involving Western and European populations. It is unclear to what extent the findings from these studies apply globally. Some studies have suggested that risk factors vary in their relationship to CHD in different populations, but these findings may not be reliable, given the small numbers of events in each study and their variable methodologies.[4] Furthermore, even if the relationship (e.g., odds ratio [OR]) of a risk factor to CHD is similar across populations, the prevalence of risk factors vary, resulting in differing population to attributable risks (PARs). Therefore, a large study using standardized methods, aimed at discovering the relationship between risk factors and CHD in a number of countries, and representing different regions and ethnic groups, was found to be necessary.

METHODOLOGY

Participants in the Study

The INTERHEART study is a large-scale, standardized, case-control study involving about 28,000 cases (with first myocardial infarction) and matched controls from 52 countries from every inhabited continent. Study participants were recruited from 262 centers from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America. The choice of countries for INTERHEART was based on a balance between a desire to represent each major region of the world and feasibility.

All patients presenting to the coronary care unit or its equivalent with first myocardial infarction (MI) within 24 hours of symptom onset were eligible for enrollment. Patients were eligible if they had characteristic symptoms plus electrocardiographic changes indicative of a new MI. Patients with cardiogenic shock or a significant chronic medical illness were excluded. Controls were age-matched (up to 5 years older or younger) and gender-matched to each case and recruited from the hospital or surrounding community. Persons with significant chronic medical illness or a previous diagnosis of heart disease or history of chest pain on exertion were excluded.

Data Collection

A questionnaire was administered in the hospital by trained staff, who collected information about demographic factors, socioeconomic status (education, income), lifestyle (smoking, leisure time, physical activity, dietary patterns), psychosocial factors (depression, locus of control, perceived stress, life events), personal and family history of cardiovascular disease, and risk factors (hypertension, diabetes

mellitus). Height, weight, waist and hip circumferences, and heart rate were determined by a standardized protocol. Although blood pressure at the time of examination was recorded in both cases and controls, these levels would be systematically affected by MI and any blood pressure–lowering treatment that had been administered. Therefore, only self-reported history of hypertension was used in the analysis.

Nonfasting blood samples (20 mL) were drawn from every individual and centrifuged within 2 hours of admission, separated into six equal volumes, and frozen immediately at –20° C or –70° C after processing. They could be obtained within 24 hours of symptom onset in two thirds of cases.

Data on smoking were missing in 1.1% of participants, hypertension in 0.6%, diabetes in 0.7%, psychosocial variables in 11%, physical activity in 1.1%, diet in 2.1%, and waist and hip measurements in 3.5%. Blood samples were available in 21,508 of 27,098 cases (79%) and controls.

Definitions

We defined current smokers as individuals who had smoked any tobacco in the previous 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than 1 year earlier. Tertiles for waist-to-hip ratio were calculated using cut-off values of 0.90 and 0.95 in men and 0.83 and 0.90 in women. Deciles and Quintiles of the ratio of apolipoprotein B (apo B)–to–apolipoprotein A1 (apo A1) were calculated using cut-off values derived from all controls (men and women). Individuals were judged to be physically active if they were regularly involved in moderate (walking, cycling, or gardening) or strenuous exercise (jogging, football, vigorous swimming) for 4 hours or more per week. Regular alcohol use was defined as consumption three or more times per week.

Statistical Methods and Analyses

The sample size calculation for INTERHEART took into consideration the sample size requirements for each participating country or region—smaller countries that are similar were clustered together. The main analyses of this study used models fitted with unconditional logistic regression, adjusted for the matching criteria. The methods used here for analyses were checked against other methods for general agreement of key results.

All statistical tests of hypotheses were two-sided. PARs and 99% (or 95%) confidence interval (CI) were calculated using the Interactive Risk Attributable Program (IRAP) software (from the National Cancer Institute, 2002).[5] For variance estimates, the method by Engel and colleagues[6] was used to assist in calculating CI after a logit transformation.

RESULTS

Following exclusion of cases not meeting inclusion criteria or with insufficient data, 12,461 cases and 14,637 controls were included in the analysis; 9459 cases (76%) and 10,851 controls (74%) were male. The overall median age of cases with first acute MI was about 9 years lower in men than in women overall; the proportion of male cases was highest in countries with a younger age of presentation of acute myocardial infarction (AMI). The highest proportion of cases with first AMI at age 40 years or younger was in men from the Middle East (12.6%), Africa (10.9%), and South Asia (9.7%) and the lowest proportion was in women from China and Hong Kong (1.2%), South America (1.0%), and central and eastern Europe (0.9%).[7]

Association of Separate and Combined Risk Factors with Myocardial Infarction

Eight risk factors (abnormal lipid levels, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, lack of consumption of fruits and vegetables and of regular physical activity) were significantly related to AMI ($P < .0001$), except alcohol, which had a weaker association ($P = .03$). After multivariate analyses, current smoking and an increased apo B-to-apo A1 ratio (top vs. lowest quintile) were the two strongest risk factors, followed by history of diabetes, hypertension, and psychosocial factors (Table 2-1).

The combination of increasing numbers of risk factors was associated with increasing risk of MI (Fig. 2-1). Hence, together, current smoking, self-reported history of hypertension, and diabetes, which could all be determined by a

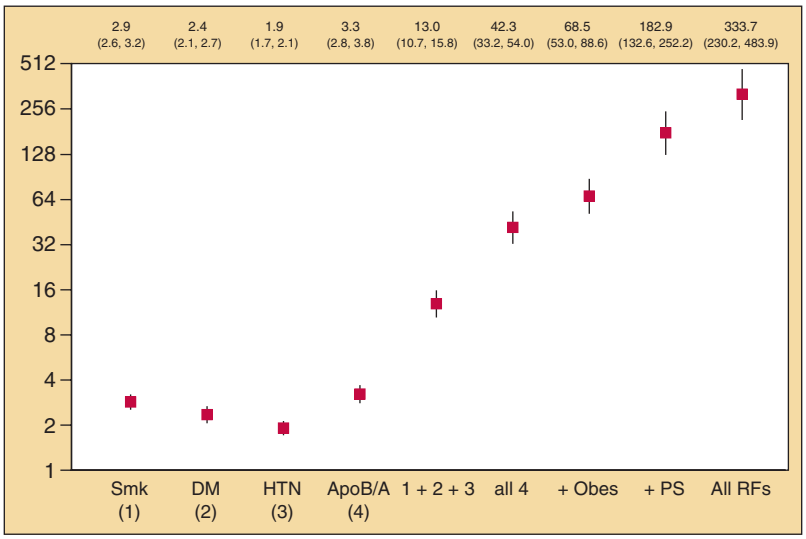

FIGURE 2–1 Risk of acute myocardial infarction associated with exposure to multiple risk factors (RFs). DM, diabetes mellitus; HTN, hypertension; Obes, obesity; PS, psychosocial factors. *(From Yusuf S, Hawken S, Ounpuu S, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries [the INTERHEART study]: Case-control study. Lancet 2004;364:937-952.)*

TABLE 2–1 Risk of Acute Myocardial Infarction Associated with Risk Factors in the Overall Population

Risk Factor	Prevalence		OR (99% CI) Adjusted for Age, Gender, and Smoking (OR 1)	PAR (99% CI)	OR (99% CI) Adjusted for All Other Risk Factors (OR 2)	PAR 2 (99% CI)
	% of Controls	% of Cases				
Current smoking*	26.76	45.17	2.95 (2.72-3.20)	—	2.87 (2.58-3.19)	—
Current + former smoking*	48.12	65.19	2.27 (2.11-2.44)	36.4 (33.9-39.0)	2.04 (1.86-2.25)	35.7 (32.5-39.1)
Diabetes	7.52	18.45	3.08 (2.77-3.42)	12.3 (11.2-13.5)	2.37 (2.07-2.71)	9.9 (8.5-11.5)
Hypertension	21.91	39.02	2.48 (2.30-2.68)	23.4 (21.7-25.1)	1.91 (1.74-2.10)	17.9 (15.7-20.4)
Abdominal obesity (2 v 1)†	33.40	30.21	1.36 (1.24-1.48)	—	1.12 (1.01-1.25)	—
Abdominal obesity (3 v 1)†	33.32	46.31	2.22 (2.03-2.42)	33.7 (30.2-37.4)	1.62 (1.45-1.80)	20.1 (15.3-26.0)
All psychosocial factors‡	—	—	2.51 (2.15-2.93)	28.8 (22.6-35.8)	2.67 (2.21-3.22)	32.5 (25.1-40.8)
Vegetables and fruits daily*	42.36	35.79	0.70 (0.64-0.77)	12.9 (10.0-16.6)	0.70 (0.62-0.79)	13.7 (9.9-18.6)
Exercise*	19.28	14.27	0.72 (0.65-0.79)	25.5 (20.1-31.8)	0.86 (0.76-0.97)	12.2 (5.5-25.1)
Alcohol intake*	24.45	24.01	0.79 (0.73-0.86)	13.9 (9.3-20.2)	0.91 (0.82-1.02)	6.7 (2.0-20.2)
Apo B-to-apo A1 ratio (2 vs. 1)§	19.99	14.26	1.47 (1.28-1.68)	—	1.42 (1.22-1.65)	—
Apo B-to-apo A1 ratio (3 vs. 1)§	20.02	18.05	2.00 (1.74-2.29)	—	1.84 (1.58-2.13)	—
Apo B-to-apo A1 ratio (4 vs. 1)§	19.99	24.22	2.72 (2.38-3.10)	—	2.41 (2.09-2.79)	—
Apo B-to-apo A1 ratio (5 vs. 1)§	20.00	33.49	3.87 (3.39-4.42)	54.1 (49.6-58.6)	3.25 (2.81-3.76)	49.2 (43.8-54.5)
All above risk factors combined¶	—	—	129.20* (90.24-184.99)	90.4 (88.1-92.4)*	129.20* (90.24-184.99)	90.4 (88.1-92.4)*

*PARs for smoking, abdominal obesity, and ApoB/ApoA1 ratio are based on a comparison of all smokers versus never, top two tertiles versus lowest tertile, and top four quintiles versus lowest quintile. For protective factors (diet, exercise, and alcohol), PARs are provided for the group without these factors.

†Top two tertiles versus lowest tertile

‡A model-dependent index combining positive exposure to depression, perceivedstress at home or work (general stress), low locus of control, and major life events, all referenced against non-exposure for all five factors.

§Second, third, fourth, or fifth quintiles versus lowest quintile.

¶The model is saturated, so adjusted and unadjusted estimates are identical for all risk factors. The odds ratio of 129·20 is derived from combining all risk factors together, including current and former smoking versus never smoking, top two tertiles versus lowest tertile of abdominal obesity, and top four quintiles versus lowest quintile of ApoB/ApoA1. If, however, the model includes only current smoking versus never smoking, the top versus lowest tertile for abdominal obesity, and the top versus lowest quintile for ApoB/ApoA1, the odds ratio for the combined risk factors increases to 333·7 (99% CI 230·2–483·9).

(From Yusuf S, Hawken S, Ounpuu S, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364:937-952.)

3-minute telephone call, increased the odds ratio for AMI to 13.01 (99% CI, 10.69 to 15.83) compared with those without these risk factors. They accounted for 53% of the PARs of AMI. Addition of the apo B-to-apo A1 ratio (top vs. lowest quintile) increased the odds ratio to 42.3 (33.2 to 54.0), and the PAR for these four risk factors together (top four quintiles of the apo B-to-apo A1 ratio vs. lowest quintile) was 75.8% (99% CI, 72.7 to 78.6).

Note that both self-reported hypertension and diabetes likely underestimate the importance of blood pressure (BP) and glucose level substantially. Therefore, it is likely that these four risk factors account for about 80% to 90% of the PARs for MI.

The addition of abdominal obesity (top two tertiles vs. lowest tertile) further increased the PAR to 80.2% (77.5% to 82.7%). In terms of a protective effect, the combined effect of fruit and vegetables and regular physical activity conferred an odds ratio of 0.60 (99% CI, 0.51 to 0.71), and the addition of smoking avoidance lowered this further to 0.21 (0.17 to 0.25), suggesting that modification of these aspects of lifestyle could potentially reduce the risk of an AMI by more than 75%.

In Women and Men

Similar odds ratios were recorded in women and men for the association of AMI with current smoking, raised lipids, abdominal obesity, composite of psychosocial variables, and vegetable and fruit consumption. However, the increased risk associated with hypertension and diabetes, and the protective effect of exercise and alcohol, seemed to be greater in women than in men.

Only former smoking was more strongly associated with MI in men compared with women. In men, smoking was associated with 42.7% of the PAR for AMI compared with 14.8% in women in the fully adjusted model. Abnormal lipids had the highest PAR in both men (49.5%) and women (47.1%), with high contributions from psychosocial risk factors (28.8% vs. 45.2%) and abdominal obesity (19.7% vs. 18.7%). Hypertension contributed to PAR in women to a greater extent (29.0%) compared with men (14.9%), partly because of a higher prevalence of hypertension in women who were about a decade older. Collectively, all nine risk factors accounted for 90% of the PAR in men and 94% in women (see Table 2-1).

Approximately two thirds of women with MI were 60 years or older compared with 40% of men with MI. Significant age differences were observed in all regions. The distribution of risk factors varied significantly between women and men controls. Overall, significantly fewer women compared with men had abnormal lipid levels (24.2% vs. 36.2%), were current (9.2% vs. 33.0%) or former (11.6% vs. 24.7%) smokers, had a high-risk diet (17.9% vs. 23.3%), performed regular physical activity (16.5% vs. 20.3%), and drank alcohol (11.2% vs. 29.1%). The proportions of women and men controls with diabetes (7.9 vs. 7.4%), abdominal obesity (33.3% vs. 33.3%), and psychosocial stress (86.4% vs. 88.8%) were similar. However, women were significantly more likely to have hypertension compared with men (28.3% vs. 19.7%).

The predicted probability of being an AMI case in someone younger than 60 years was substantially higher among men compared with women (60.6% vs. 33.0%; difference of 27.6%), decreasing to 23.2% after adjustment for regional differences and to 4.7% after adjustment for all nine risk factors and region. Thus, more than 80% of the earlier age of first MI in men compared with women is explained by the differences in the distribution of the nine risk factors. This suggests that the higher levels of some risk factors in men of younger ages can largely explain the earlier age of acute MI in men.[1]

Different Ages

Smoking, adverse lipid profile, hypertension, and diabetes had a greater relative effect on the risk of AMI in younger (≤55 years in men and ≤65 years in women) than older individuals. Overall, abnormal lipids were the most important risk factor with respect to PARs in younger and older individuals. Collectively, the nine risk factors accounted for significantly greater ($P < .0001$) PARs in younger than older individuals; these patterns were consistent in males and females.

Different Geographic Regions

In all regions, the nine risk factors accounted for between 75% and almost all PARs for AMI; the relative importance of every risk factor varied largely in relation to its prevalence. Raised lipid levels, smoking, and psychosocial factors were the most important risk factors in all regions worldwide. Noteworthy abdominal obesity was associated with a PAR greater than that of smoking in Western Europe, North America, and Australia and New Zealand (representing high- income countries) and Southeast Asia (mostly middle-income countries). A similar pattern was seen for Africa, but most of these data were drawn from South Africa, which is a middle-income country. However, obesity was less important in other parts of the world, where it is less prevalent. For example, obesity accounted for only 5.5% of the PAR in China compared with 35.8% for smoking; 41% of male and 4% of female controls in China smoked. Subdividing the population by ethnic origin, these nine risk factors accounted for a very high proportion of PARs in every ethnic group (Europeans, 86%; Chinese, 90%; South Asians, 92%; black Africans, 92%; Arabs, 93%; and Latin Americans, 90%).

Measurement and Analysis of Psychosocial Factors

The INTERHEART study instrument included a standard yet simple set of questions that inquired categorically about psychosocial conditions within the previous 12 months. Stress was assessed with two single-item questions relating to stress at work and home. Measures were also made of the generalized locus of control. This is the perceived ability to control life circumstances. Symptoms of depression were also assessed by asking whether the participant had felt sad, blue, or depressed for 2 weeks or more in a row during the past 12 months and, if yes, graded by a set of seven no-yes questions.

A higher prevalence of all measures of stress was reported by those with AMI ($P < .0001$). Permanent work stress was experienced by twice as many cases than controls after adjustment for age, gender, geographic region, and smoking. The PAR among those working was 9% (99% CI, 1 to 18). Further adjustment for education and income, hypertension, diabetes, level of physical activity, waist-to-hip ratio, dietary patterns, alcohol, or raised plasma lipid levels did not alter these results to a significant degree.

High locus of control was a significant protective factor, 0.72 (99% CI, 0.65 to 0.79) in the fourth quartile relative to the first and 0.75 (99% CI, 0.65 to 0.86) after adjustment for age, gender, geographic region, and all risk factors, including smoking. The PAR for low locus of control was 16%.

In terms of depression measures, more patients reported feeling sad, blue, or depressed for more than 2 weeks or more in a row (odds ratio, 1.55 [1.42 to 1.69]; this difference did not change substantially after adjustment for other factors. The PAR associated with sadness and depression was 9%.

The combination of all psychosocial factors—exposure to general stress, financial stress, stressful life events, depression, and low locus of control—resulted in an estimated PAR of 29% (22% to 35%) after adjustment for age, gender, geographic region, and smoking. Further adjustment for all risk factors (education and income, hypertension, diabetes, level of physical activity, waist-to-hip ratio, dietary patterns, alcohol, or raised plasma lipid levels) changed the PAR estimate to 33% (25% to 41%). These findings were consistent across regions, in different ethnic groups, and in men and women.

Specific Risk Factors

Smoking

Almost 80% of control women never smoked during the past 12 months and less than 10% were current smokers. Younger (≤65 years) women were slightly more likely to have smoked at any time compared with older (>65 years) women (21.9% vs. 19.2%), and were more likely to be current smokers (11.1% vs. 6.5%). Prevalence of current smoking was fairly high (>20%) among younger women in three regions (North America, Western Europe, and Africa), very low (<5%) in Asia and the Middle East, and intermediate (10% to 20%) in Australia, New Zealand, Eastern and Central Europe, and Latin America. Among older women, the prevalence of current smoking was very low in most regions. The pattern of smoking in female controls differed substantially from that in male controls, of whom approximately one third were current smokers. The prevalence of smoking (current or past) was similar between younger (≤55 years) and older groups (>55 years age) of men (57.3% vs. 58.9%). The highest rates of current smoking among young male controls were reported in China and Hong Kong, Eastern and Central Europe and Africa (all >50%). The lowest rates were in North America, Australia, and New Zealand (<25%).[8]

Current smoking was associated with a greater risk of nonfatal AMI (OR, 2.95; 95% CI, 2.77 to 3.14; $P < .0001$) compared with never smoking: risk increased by 5.6% for every additional cigarette smoked (Fig. 2-2). The OR associated with former smoking fell to 1.87 (95% CI, 1.55 to 2.24) within 3 years of quitting. A residual excess risk remained 20 years or more after quitting (OR, 1.22; 95% CI, 1.09 to 1.37). Smoking beedies (indigenous to South Asia) alone was associated with increased risk (OR, 2.89; 95% CI, 2.11 to 3.96), similar to that associated with cigarette smoking. Chewing tobacco alone was associated with an OR of 2.23 (95% CI, 1.41 to 3.52) and smokers who also chewed tobacco had the highest increase in risk (OR, 4.09; 95% CI, 2.98 to 5.61). Second-hand smoke was associated with a graded increase in risk related to exposure: OR = 1.24 (95% CI, 1.17 to 1.32) in individuals who were least exposed (1 to 7 hours/week) and 1.62 (95% CI, 1.45 to 1.81) in people who were most exposed (>21 hours/week). Young male current smokers had the highest PAR (58.3%; 95% CI, 55.0 to 61.6) and older women the lowest (6.2%; 95% CI, 4.1 to 9.2). The PAR for exposure to second-hand smoke for more than 1 hour/week in never-smokers was 15.4% (12.1 to 19.3).

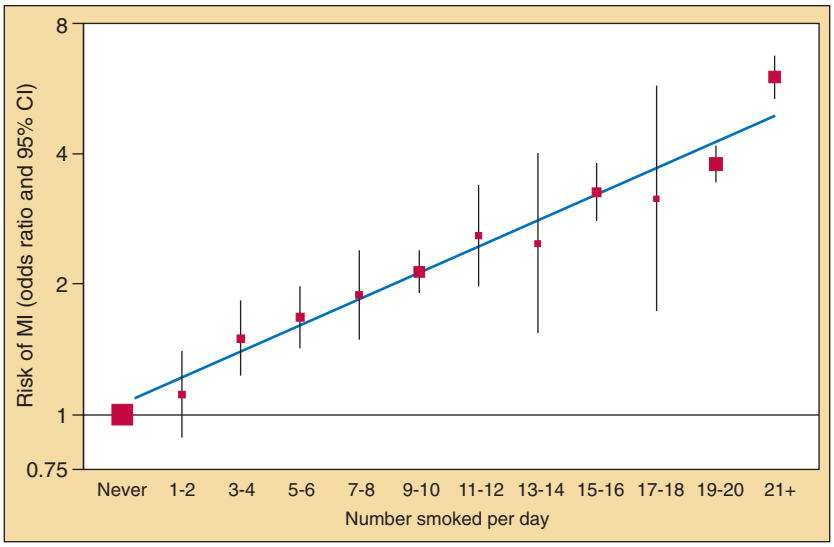

FIGURE 2–2 Risk of AMI with increasing number of cigarettes smoked compared with never-smokers. *(From Teo KK, Ounpuu S, Hawken S, et al: Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: A case-control study. Lancet 2006;368:647-658.)*

Obesity

Analysis of the INTERHEART study compared three markers —waist-to-hip ratio, waist circumference, and body mass index (BMI)—for their ability to predict acute myocardial infarction.[9]

Striking variations were seen in the proportion of those with obesity (BMI > 30 kg/m^2) or who were overweight (>25 kg/m^2) in the various regions. However, the pattern across regions was different if data for the waist-to-hip ratio (WHR) was used to define obesity. The difference between cases and controls was more pronounced with WHR than with BMI.

BMI showed a modest and graded association with MI (OR, 1.44; 95% CI, 1.32 to 1.57, before adjustment) that was reduced after adjustment for WHR (OR, 1.12; 95% CI, 1.03 to 1.22) and nonsignificant after adjustment for other risk factors (OR, 0.98; 95% CI, 0.88 to 1.09). For WHR, the OR for every successive quintile was significantly greater with each quintile, from 1.15 (95% CI, 1.05 to 1.26) in the second quintile to 2.53 (95% CI, 2.31 to 2.74) in the fifth quintile after adjustment for age, gender, region, and smoking. Waist (adjusted OR, 1.77; 95% CI, 1.59 to 1.97) and hip (OR, 0.73; 95% CI, 0.66 to 0.80) circumferences were both significant after adjustment for BMI ($P < .0001$, top vs. bottom quintiles) and WHR and waist and hip circumferences after adjustment for other risk factors (OR for top vs. lowest quintiles, 1.75, 1.33, and 0.76, respectively). The areas under the receiver operator curves of BMI (0.559), waist circumference (0.571), and hip circumference (0.554) were smaller than that of WHR (0.601).

Of the three measures compared, BMI showed the weakest association with myocardial infarction risk in all ethnic groups, with no significant relationship in South Asians, Arabs, and mixed race Africans.

By contrast, the WHR showed a significant association with myocardial infarction in all ethnic groups, and was the strongest marker in six of the eight ethnic groups. Waist circumference was intermediate between WHR and BMI in its association with myocardial infarction in most ethnic groups apart from Chinese and black Africans, in whom waist circumference was the strongest predictor. Thus, a marker of abdominal obesity was better than BMI as a predictor of myocardial infarction in all ethnic groups.

The WHR had a graded and highly significant association with MI risk worldwide. Redefinition of obesity based on WHR instead of BMI increases the estimate of AMI attributable to obesity in most ethnic groups.

Lipids, Lipoproteins, and Apolipoproteins

INTERHEART analyses have found that the apo B-to-apo A1 ratio had the highest PAR (54%), greater than that of the total cholesterol (TC)–to–high-density lipoprotein cholesterol (HDL-C) ratio (32%), and the highest OR for each 1 standard deviation (SD) increase (OR, 1.59; 95% CI, 1.53 to 1.64) of all risk factors and lipid markers measured. For a 1-SD increase, apo A1 had a significantly better OR of 0.67 (95% CI, 0.65 to 0.70) compared with HDL-C (OR, 0.85; 95% CI, 0.83 to 0.88; $P < .001$); the apo B and non–HDL-C had an OR of 1.32 (1.28 to 1.36) and 1.21 (1.17 to 1.24), respectively. Correction for regression dilution bias increased the PAR for these ratios by 10% to 15%. The nonfasting apo B-to-apo A1 ratio is the most powerful lipoprotein index of risk of AMI. This holds worldwide, in all ethnic groups, in both genders and at all ages, accounting for over half of these cases.

Dietary Patterns

The dietary patterns were assessed using a simple, 19-item, qualitative food group frequency questionnaire (FGFQ). This FGFQ was designed as a generic questionnaire that could be used in many countries despite regional differences in intake of a specific food item in a category. Three major dietary patterns were identified using factor analysis—Oriental, Western, and prudent (high in fruit and vegetables). Food items considered to be predictive (meat, salty snacks, fried foods) or protective (fruits and green leafy vegetables, other cooked or raw vegetables) of CVD were used to generate a dietary risk score (DRS).

There was an inverse association between the prudent pattern and AMI risk. Compared with the first quartile, the adjusted OR for the second quartile was 0.78 (95% CI, 0.69 to 0.88); third quartile, OR, 0.66 (95% CI, 0.59 to 0.75); and fourth quartile, OR, 0.70 (95% CI, 0.61 to 0.80; P for trend < .001). The Western pattern showed a positive association with AMI risk. Compared with the first quartile, the adjusted OR for the second quartile was 0.87 (95% CI, 0.78 to 0.98); third quartile, OR, 1.12 (95% CI, 1.00 to 1.25) and fourth quartile, OR, 1.35 (95% CI, 1.21 to 1.51; P for trend < .001). The Oriental pattern, however, demonstrated no relationship with AMI. Compared with the first quartile, the OR of a

dietary risk score (derived from meat, salty snacks, fried foods, fruits, green leafy vegetables, cooked vegetables, and other raw vegetables) increased with each quartile; the second quartile OR was 1.29 (95% CI, 1.17 to 1.42), third quartile OR was 1.67 (95% CI, 1.51 to 1.83), and fourth quartile OR was 1.92 (95% CI, 1.74 to 2.11; P for trend < .001). The PAR of AMI for the top three quartiles compared with the bottom quartile of the dietary risk score was 30%. An unhealthy dietary intake, assessed by a simple dietary risk score increases the risk of AMI globally, and accounts for about 30% of the PAR.

Regional Analyses

South Asian

South Asians have high rates of AMI at younger ages (mean, 53.0 SD at 11.4 years) compared with individuals from other countries (mean, 58.8 SD at 12.2 years; $P \leq .001$). Protective factors were lower (exercise, daily intake of fruits and vegetables, and alcohol consumption once/week, 10.7% vs. 26.9%), and some harmful factors were more common (apo B-to-apo A1 ratio, history of diabetes). The similar OR for the risk factors explained a high and similar degree of PARs in South Asia compared with other countries. When stratified by age, South Asians had more risk factors at ages younger than 60 years. After adjusting for all nine risk factors, the predictive probability of classifying an AMI patient as being younger than 40 years was similar in individuals from South Asian countries and those from other countries. Higher risk factor levels can largely explain the earlier onset of MI in South Asians at younger ages.[10]

Latin America

In this region, persistent psychosocial stress, history of hypertension, current smoking, increased WHR, and increased apo B-to-apo A1 ratio were associated with a higher risk of AMI. Daily consumption of fruits or vegetables and regular exercise reduced the risk of AMI. Abdominal obesity, abnormal lipid levels, and smoking were associated with high PARs of 48.5%, 40.8%, and 38.4%, respectively. Collectively, these risk factors accounted for 88% of PARs.[11]

Africa

The relationship between risk factors and AMI were investigated in Africa in three ethnic subgroups (black, people of color, and Europeans and other Africans) and compared with those found in the overall INTERHEART study. Relationships between common CVD risk factors and AMI were found to be similar to those in the overall INTERHEART study. Modeling five risk factors (smoking history, diabetes history, hypertension history, abdominal obesity, and apo B-to-apo A1 ratio) yielded a PAR of 89.2% for AMI. The risk for AMI increased with higher income and education in the black African group in contrast to findings in the other groups. A history of hypertension revealed a higher MI risk in the black African group than in the overall INTERHEART group. Known CVD risk factors accounted for about 90% of MIs observed in African populations, which is consistent with the overall INTERHEART study. Contrasting gradients found in socioeconomic class, risk factor patterns, and AMI risk in the ethnic groups suggest that they are at different stages of the epidemiologic transition.[12]

SUMMARY OF FINDINGS

The key findings of the INTERHEART study are summarized in Box 2-1. Nine simple risk factors account for over 95% of the PAR globally, with results qualitatively consistent for all regions, ethnic groups, genders, and age groups. The strong dose-response relationship observed emphasizes the potential major impact of modification of diet, increasing physical activity, and tobacco cessation. Thus, lifestyle modification should be the foundation for prevention efforts.

Other new findings of importance include the following:

1. Simple measures of stress, including stress at home or work, financial stress, stress associated with major life events, and markers of depression, were strongly associated with AMI risk.
2. All forms of tobacco exposure, including smoking cigarettes or beedies, chewing tobacco, and second-hand smoke have a strong and graded relationship with AMI.
3. Abdominal obesity, particularly WHR, was a better predictor of AMI risk than BMI.
4. The nonfasting apo B-to-apo A1 ratio was a better predictor of AMI compared with any marker separately or the TC/HDL ratio.
5. Simple measures of dietary pattern and dietary risk score showed a strong and graded relationship with AMI.
6. The lower MI burden in women at younger ages is largely explained by a lower risk factor burden.
7. The findings were universally applicable.

FUTURE DIRECTIONS

The major findings of the INTERHEART study were that acute myocardial infarction can be attributed to known risk factors. This suggests that the major emphasis in research should be to understand why known risk factors develop in some individuals and some populations—search for the causes of the causes—and to identify approaches to prevent their development or reduce them. It is likely that societal, environmental, and biologic causes contribute to the development of risk factors in populations and individuals. An understanding of the societal factors that affect the development of risk factors (e.g., urbanization, food and tobacco

BOX 2-1 Key Findings

Summary of Main Findings

1. Nine simple risk factors account for over 90% of PARs globally.
2. The findings are consistent in all regions, ethnic groups, genders, and age groups.
3. Lipids (apo B-to-apo A1 ratio) and smoking tobacco account for about two thirds of the global risk of AMI.
4. Modification of lifestyle (diet, increasing physical activity, and tobacco cessation) has potential for major global impact.

Summary of Additional Findings

1. Simple measures of symptoms of stress and depression were strongly associated with MI.
2. All forms of tobacco exposure, including smoking cigarettes or beedies, chewing tobacco, and second-hand smoke have a strong and graded relationship with MI.
3. Abdominal obesity, particularly WHR, was a better predictor of AMI risk than BMI.
4. Nonfasting apo B-to-apo A1 ratio was a better predictor of AMI compared with any marker separately or the TC/HDL ratio.
5. Simple measures of dietary pattern and a dietary risk score showed a strong and graded relationship with AMI.
6. Lower MI burden in women at younger ages is largely explained by a lower risk factor burden.

policies, shifts in occupation from energy-expending jobs to sedentary ones) could lead to new approaches to prevent the development of risk factors (primordial prevention), which in turn could reduce coronary heart disease substantially. Similarly, understanding the factors in the environment (e.g., pollution, urban planning, use of car vs. public transit or walking) could lead to different approaches to increasing physical activity and reducing obesity.

Research thus far into the genetic markers of CHD has been disappointing. However, given that nine risk factors discussed account for most cases of CHD, it may be strategic to try to understand the genetic associations for each of these risk factors, rather than to relate the genetic markers independently to CHD. It is very likely that any genetic marker exerts its influence by affecting the major risk factors. Thus, future research should focus on gene-environment interactions that influence the risk factors. In recent years, there has been a hunt for putative novel risk markers (e.g., inflammatory markers, homocysteine). The nine simple risk factors described account for most (>95%) of the PARs for AMI, so even if some of the novel risk factors are actual independent predictors of AMI, their role is likely to be modest, as a confounder or consequence of these risk factors. Therefore it is unlikely that research into novel risk factors will identify new therapeutic targets that will substantially modify the underlying process of atherosclerosis and thrombogenesis.

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CHAPTER 3

Results from the Reduction of Atherothrombosis for Continued Health (REACH) Registry

Telly A. Meadows, Deepak L. Bhatt, and P. Gabriel Steg

The clinical manifestations of atherothrombotic disease include strokes and transient ischemic attacks, critical limb ischemia, angina, and the full spectrum of acute coronary syndromes (Fig. 3-1). The benefits of lifestyle modifications and aggressive risk reduction therapies for prevention of these ischemic events are well established.[1-3] Prior studies investigating risk factors associated with atherothrombosis have had several limitations, including confinement to a single geographic locale or ethnic group, a particular subtype of atherothrombosis (i.e. coronary artery disease [CAD] only, cardiovascular disease [CVD] only, or peripheral artery disease [PAD] only), and only those patients participating in clinical trials. The objectives of the ***RE***duction of ***A***therothrombosis for ***C***ontinued ***H***ealth (REACH) registry were several, including an investigation of traditional and emerging atherothrombotic risk factors and a comparison of treatment modalities in individuals with various risk factor profiles. Additionally, the registry allowed for a global assessment of the extent of atherothrombosis and its associated clinical outcomes in a geographically and ethnically diverse population deemed high risk for or with stable atherothrombotic disease.[4] Importantly, the results aimed to provide an accurate, contemporary reflection of actual real-world practice.

The international, prospective, observational registry enrolled from December 2003 to June 2004 a total of 67,888 outpatients 45 years or older from 44 countries, consisting of 5473 physician practices.[4] The patient population included individuals with three or more atherothrombotic risk factors and patients with established CAD, CVD, or PAD. The rate of symptomatic polyvascular disease was 15.9% in those with established atherothrombosis (Fig. 3-2).

Risk factors could include diabetes mellitus, hypertension, hypercholesterolemia, smoking, advanced age, asymptomatic carotid artery stenosis 70% or more, diabetic nephropathy, and low ankle-brachial index (ABI < 0.9). Baseline data collected on each participant at enrollment included demographic information, employment status, medical history, risk factors, and medical therapies. Clinical events, data regarding hospitalizations, employment status, and medical treatments were recorded at 1- and 2-year follow-up.

BASELINE DEMOGRAPHICS AND TREATMENT OF TRADITIONAL RISK FACTORS

The prevalence of classic risk factors for CAD, CVD, and PAD was consistent worldwide and included high rates of hypertension, diabetes mellitus, and hyperlipidemia.[5-8] Hypertension was the most prevalent risk factor, found in 81.8% of the population. The proportion of participants with hyperlipidemia was 72.4%, and 44.3% of patients had diabetes mellitus. Although not as common as these three risk factors, the registry revealed the global extent of obesity (overall rate of 29.9% as defined by body mass index [BMI]; 46.5% as defined by waist circumference) and confirmed its emergence as a major health care problem worldwide. Although similar in most geographic locales, the rate of obesity was highest in North America, occurring at an alarming rate of 36.5%. This finding should serve as advance notice to the entire world, particularly developing nations, regarding the importance of patient and physician education on lifestyle measures to combat this growing epidemic.

The REACH registry also demonstrated the current divide between actual clinical practice and guideline-recommended treatments for patients with or at risk for atherothrombotic disease (Fig. 3-3). This gap was universally present throughout the world, regardless of disease subtype or physician specialty. The rates of undertreated hypertension, undiagnosed hyperglycemia, and impaired fasting glucose (in individuals not known to be diabetic) were 50%, 4.9%, and 36.5%, respectively.[5] Similarly, the rates of elevated cholesterol levels at baseline were equally impressive, varying

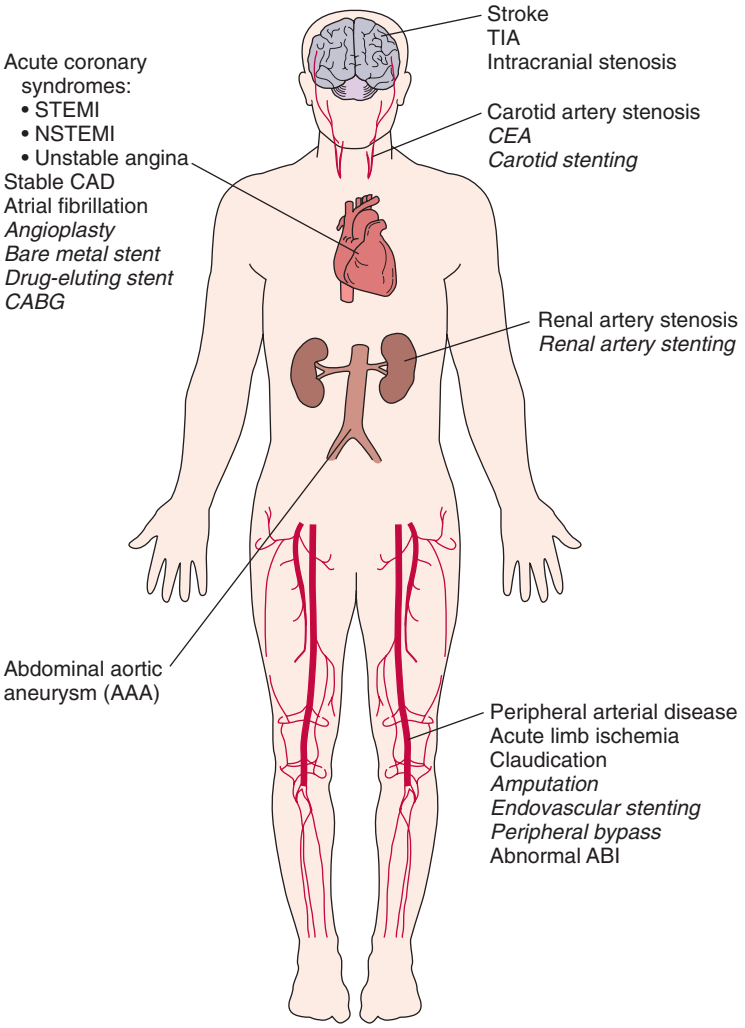

FIGURE 3–1 Clinical manifestations of atherothrombotic disease. CEA, carotid endarterectomy; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. *(From Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 2007;100:1261-1275.)*

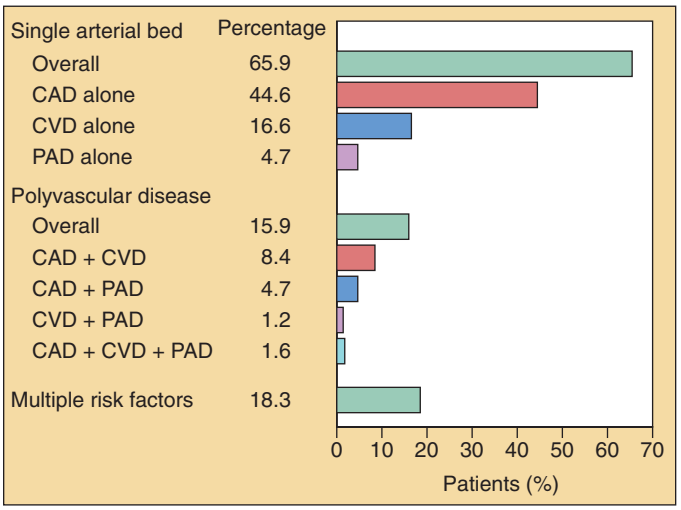

FIGURE 3–2 Prevalence of polyvascular disease in the REACH registry. *(From Bhatt DL, Steg PG, Ohman EM, et al: International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-189. Copyright © 2006, American Medical Association. All rights reserved.)*

among geographic regions from as low as 24.4% in Australia to as high as 64.4% in Eastern Europe. The overall use of statins was 69.4%; however, this differed depending on the disease subtype, ranging from 56.4% in those with cerebrovascular disease to 76.2% in those with coronary artery disease. The use of antiplatelet therapy was 78.6% in the total population, whereas only 53.9% of those patients at risk for atherothrombotic disease were on this therapy. Although medication use was suboptimal worldwide, there was some variation of use depending on geographic locale and physician specialty. Prescription of statin therapy ranged from as low as 44.6% in Japan to as high as 82.4% in the Middle East. Among physicians, cardiologists were most likely to prescribe statin and antiplatelet therapy.

The disparities between the guideline-recommended therapies and the real-world care of patients with established atherothrombotic disease were slightly diminished in those individuals with prior history of revascularization. Among the 18,467 patients in the REACH registry with a history of transient ischemic attack (TIA) or ischemic stroke, there was a significantly increased use of antiplatelet agents (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.3 to 1.5; $P < .0001$) and statins (OR, 1.8; 95% CI, 1.6 to 2.0; $P < .0001$) in those who had a history of carotid endarterectomy.[9] Similarly, in the 40,450 patients with established CAD, the use of secondary medical preventive therapies was influenced by the patient's coronary revascularization history.[10] In those with a

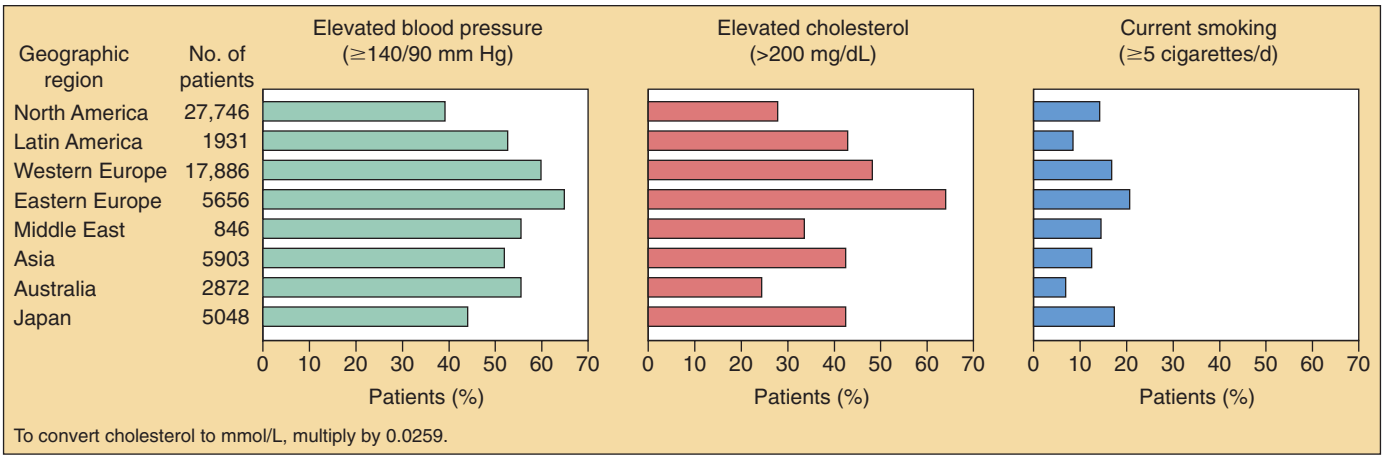

FIGURE 3–3 Global undertreatment of cardiovascular risk factors in the REACH registry. *(From Bhatt DL, Steg PG, Ohman EM, et al: International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-189. Copyright © 2006, American Medical Association. All rights reserved.)*

history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), the use of antiplatelet therapy and lipid-lowering therapy was significantly higher than that observed in those with no prior history of any coronary revascularization procedure. Although prior history of revascularization in these specific patient subsets did translate into better compliance with recommended secondary preventive therapies, their overall use still remained suboptimal.

Because of enrollment delays, baseline data on participants from Japan were analyzed separately from the data from the rest of Asia and published later.[11] Although the Japanese patients in the registry shared many similarities with the global population, there were some significant distinctions seen in this population. The Japanese patients recruited in REACH had higher rates of cerebrovascular disease than the global cohort (39.2% vs. 27.8%). When using definitions outlined by the National Cholesterol Education Program (NCEP), obesity rates in Japan were markedly lower than those seen in North America (10.6% vs. 36.5%). However, Japanese obesity rates increased to 42.1% with the application of the Japanese guidelines for obesity (waist circumference, ≥85 cm for men; ≥90 cm for women).[11]

Both the use and type of secondary preventive therapies prescribed by Japanese physicians were distinctly different than those seen elsewhere. The use of any antiplatelet agent for primary prevention was markedly lower in Japan than that seen worldwide (21.3% vs. 53.9%).[11] Similarly, the use of aspirin in patients with established atherothrombotic disease was also lower in Japan as compared to the rest of the REACH cohort (54.7% vs. 67.4%), whereas the use of other antiplatelet agents was higher in Japan than elsewhere (31.1% vs. 24.7%). In addition to these differences with aspirin therapy, there was also a marked difference in the use of lipid-lowering agents, including statins, in Japan as compared with the global cohort (50.8% vs. 75.2%).

Among U.S. patients with PAD in the REACH registry, there also appeared to be ethnic-specific differences in the rate and treatment of classic cardiovascular risk factors.[12] In the United States, African Americans with PAD were more likely to have hypertension, diabetes mellitus, morbid obesity, and isolated PAD than their white counterparts. Although African Americans with PAD were more likely to have some risk factors for atherosclerosis, they were more likely to have uncontrolled hypertension (blood pressure [BP] ≥ 140/90 mm Hg, 54.9% vs. 38.1%; $P < .0001$) and hyperlipidemia (cholesterol >200 mg/dL, 41.7% vs. 24.9%; $P < .0001$) than non-Hispanic whites with PAD. Despite these differences, there were similar cardiovascular outcomes between these two groups at 1-year follow-up. Presumably, these disparities in the undertreatment of blood pressure and cholesterol would translate into adverse clinical outcomes if persistently present over a longer time span.

CLINICAL OUTCOMES

The clinical outcomes observed in the REACH registry illustrated the ramifications of having stable atherosclerotic disease. One-year outcomes data were available for 95.2% of the participants originally enrolled in the registry.[13] Overall, the cardiovascular (CV) death, myocardial infarction (MI), or stroke rate at 1 year was 4.24% (Fig. 3-4). Despite widespread use, albeit suboptimal, of contemporary medical therapies, individuals with established atherothrombotic disease had a 1 in 7 chance of having a major event (CV death, MI, and stroke) or hospitalization for an event or revascularization procedure within 1 year. Cardiovascular mortality was highest in patients with PAD, with a 1-year event rate of 2.51%. Patients with CAD had the highest rates of nonfatal MI (1.44%), whereas those with CVD had the highest rates of nonfatal stroke (3.70%) at 1 year. There was a 5% 1-year event rate for coronary revascularization in those with CAD, whereas more than 10% of patients with PAD required a lower extremity revascularization procedure or amputation within 1 year. The socioeconomic impact of having atherothrombotic disease is also substantial. At 1-year follow-up, almost 50% of individuals employed at baseline who had suffered an ischemic event were no longer working.

The registry also showed how the magnitude of atherosclerotic disease burden affects an individual's risk for ischemic events. Given the significant overlap between disease involvement in various vascular beds, patients with atherosclerosis in multiple vascular territories were counted in multiple groups. For example, a patient with a documented history of both myocardial infarction and stroke at the time of enrollment into the registry would be counted in both the CAD and CVD groups in the data analysis. The analysis of cross risk, defined as the risk of an ischemic event in an arterial bed separate from those affected at the time of enrollment, was performed by evaluating predefined cohorts with atherosclerosis isolated to a single vascular bed or multiple arterial beds (Table 3-1). Although the risk of CV death, MI, or stroke at 1 year was 4.69% for those patients with established CAD, PAD, or CVD, those with multiple risk factors only had event rates less than half (2.15%) of those seen in those with symptomatic disease.[13] Rates of CV death, MI, or stroke rose sharply with more extensive burden of atherothrombosis, from 2.2%

TABLE 3–1 Cardiovascular Event Rates at 1 Year by Vascular Bed Involvement (%)*

Event	Single Arterial Bed	CAD Only	CVD Only	PAD Only	Polyvascular Disease	CAD + CVD	CAD + PAD	PAD + CVD	CAD + PAD + CVD
CV death	1.58	1.58	1.62	1.37	2.78	2.40	3.23	2.15	3.93
Nonfatal MI	1.12	1.37	0.51	1.00	1.60	1.72	1.49	1.08	1.83
Nonfatal stroke	1.54	0.86	3.60	0.81	3.07	3.54	1.24	4.93	4.39
CV death, MI, or stroke	4.07	3.64	5.54	3.06	7.05	7.35	5.54	7.76	9.21

*Adjusted for gender and age.

Adapted from Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197-1206.

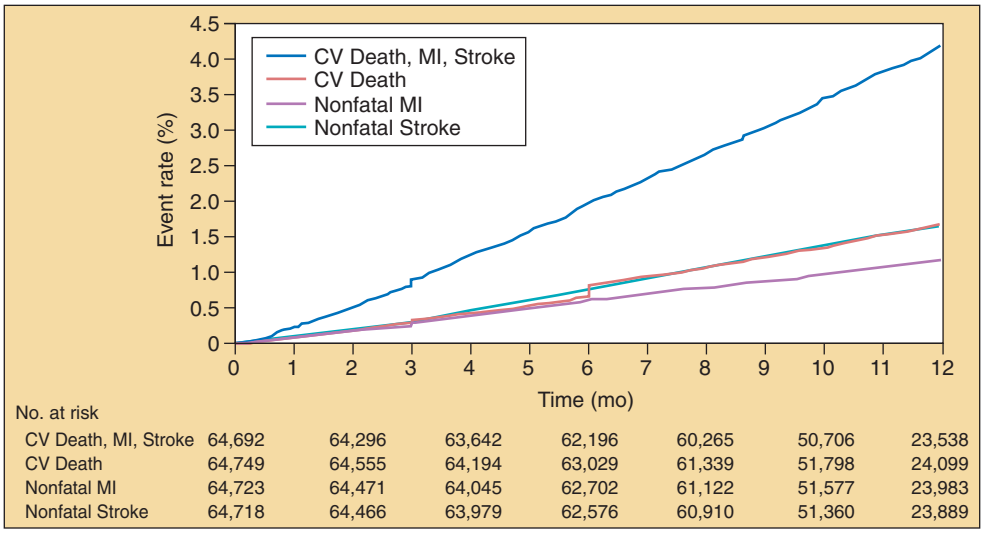

FIGURE 3–4 One-year cardiovascular event rates in the REACH registry. *(From Steg PG, Bhatt DL, Wilson PW, et al: One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197-1206. Copyright © 2007, American Medical Association. All rights reserved.)*

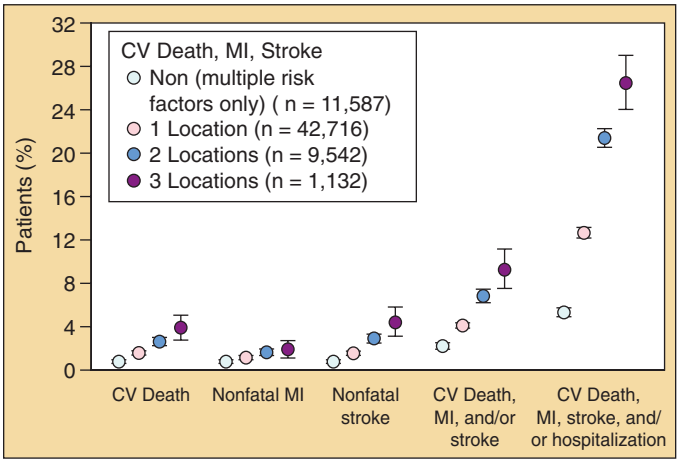

FIGURE 3–5 Cardiovascular event rates by burden of atherosclerosis in the REACH registry. *(From Steg PG, Bhatt DL, Wilson PW, et al: One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197-1206. Copyright © 2007, American Medical Association. All rights reserved.)*

in patients with risk factors only to 9.2% in patients with established disease in all three vascular locations (Fig. 3-5). In individuals with established atherothrombotic disease, those with disease isolated to a single vascular bed had approximately half the rate of major CV events compared to those with polyvascular disease. Due to the preponderance for ischemic events, the aggressive use of medical therapies to reach established target goals is paramount in patients with established atherothrombotic disease, especially in those with polyvascular disease.

Although the cardiovascular outcomes were similar across the various geographic regions studied in the registry, there were some variations (Table 3-2). The lowest rates of cardiovascular death and myocardial infarction were seen in patients from Japan, whereas the region with the lowest rate of nonfatal strokes was Australia. In comparison to the rest of Asia, Japan generally had lower rates for all events. Overall, Eastern Europe had the highest 1-year combined CV death, MI, or stroke event rate, at 7.62%, and Australia had the lowest rate of this combined triple end point, at 3.13%. Nonetheless, the combined end point of CV death, MI, or stroke surpassed the expected 3% 1-year event rate in every geographic region studied.

Given the inherent qualities of a registry analysis, there are several limitations to the REACH study.[5,13,14] The external validity of this study may be somewhat limited, particularly because this was a non–population-based registry. Even though physicians were asked to recruit consecutive patients, it is difficult to ascertain the impact of recruitment bias. In contrast to randomized controlled studies, the registry did not keep track of compliance with these instructions through the use of log books. Compliance and contraindications to pharmacologic therapies were also not documented, which limits the estimation of its influence on medication use or lack thereof. Similarly, the impact of economic limitations on these same issues was not factored into the overall

TABLE 3–2 Cardiovascular Outcomes at 1 Year by Geographic Region (%)*

Event	Region								
	Global	North America	Latin America	Western Europe	Eastern Europe	Middle East	Asia	Australia	Japan
CV death	1.65	1.50	2.23	1.75	2.90	2.71	2.04	1.41	0.74
Nonfatal MI	1.14	1.29	0.96	1.07	1.25	2.66	0.82	0.91	0.80
Nonfatal stroke	1.66	1.18	2.74	1.53	3.78	2.21	2.60	0.94	1.80
CV death, MI, or stroke	4.24	3.70	5.76	4.14	7.62	6.99	5.27	3.13	3.22

*Adjusted for gender and age.

Adapted from Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197-1206.

findings. Despite the breadth of geographic locales and extent of ethnic diversity included in the data set, there were important areas that were not included and/or underrepresented in the registry, such as Chinese and African populations. Also, there is the possibility of increased compliance with guideline-recommended therapies and interventions by those physicians and subjects who chose to participate in the registry compared with those who did not make this choice. However, this would have likely resulted in an underestimation in both the event rates observed at 1 year and the undertreatment of atherosclerotic risk factors seen at baseline. Even though the follow-up rates were impressive for the size and international extent of the registry, there was a 5% loss of follow-up rate at 1 year, which theoretically could have resulted in minor miscalculations in the event rate estimates.[13]

In summary, the REACH registry demonstrated that there are considerable gaps between the recommended use of risk-reducing therapies and interventions and actual current practice in the real world. From a global perspective, traditional cardiovascular risk factors are consistently present and they account for the greatest proportion of risk for atherothrombotic disease. However, the ever-increasing obesity epidemic that is currently plaguing the industrialized nations of the world, particularly North America, almost guarantees its emergence as a major cause of atherothrombotic disease on a global scale. Despite these facts, a substantial number of individuals were not at targeted goals for their blood pressure, cholesterol, glucose, or weight. Although considered to be a "stable" cohort of outpatients with atherothrombotic disease, short-term ischemic events in this population were relatively high, particularly in those with polyvascular disease. Atherosclerosis is a systemic process that can manifest itself in any vascular territory in the body. As a result, individuals thought to have disease isolated to a single particular vascular bed are at increased risk of morbidity and mortality from ischemic events occurring in other presumably nonaffected vascular territories. As such, physicians and patients must be cognizant of the need for a more comprehensive approach toward treatment of atherothrombotic diseases. There must be a collaborative effort from various specialists to improve patient awareness, education, and adherence to established evidence-based therapies in hopes of preventing the ill effects of CAD, CVD, and PAD in this particularly susceptible population.

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CHAPTER 4

Historical Perspective and Lessons Learned from the Euro Heart Surveys on Acute Coronary Syndromes

David Hasdai, Anselm K. Gitt, and Jean-Pierre Bassand

The Euro Heart Survey program was launched by the European Society of Cardiology (ESC) around the year 2000 to assess variations in management and treatment of cardiovascular disease (CVD) across Europe, particularly with regard to diagnostic procedures and treatments. Both the incidence of CVD and access to medical care are highly variable throughout Europe. Reports have shown that for a given age group, the risk of dying from CVD was five times higher in eastern European countries as compared with western European countries such as France, Italy, or Spain (Fig. 4-1).[1] This huge difference in the prevalence of CVD is linked to several factors, including the higher prevalence of risk factors such as smoking, hypertension, obesity, and diabetes in eastern compared with western European populations. The common denominator of this higher incidence of risk factors and CVD is probably unfavorable economic conditions. As a result, the countries where the incidence of CVD is highest are also those that offer the least adequate health care to their citizens. Differences in the rate of CVD and the dynamics of this rate over time have been recorded in several reports coordinated by the ESC.[2,3] These reports have consistently shown that as the European population ages, more people are surviving a first manifestation of CVD, particularly coronary artery disease (CAD). Similarly, the number of people suffering from CVD and requiring treatment is increasing steadily over time. If the rate of hospital discharge with a primary diagnosis of CVD, ischemic heart disease, or cerebrovascular disease is taken as an indicator of the burden of CVD in Europe, it seems that there has been a gradual and steady increase since the early 1990s. The standardized rate of CVD mortality is decreasing in men and women in Europe, but there is a trend toward an increase in the countries of the Commonwealth of Independent States (CIS; see Fig. 4-1). (The CIS is made up of former Soviet republics.)

Since 1990, the number of hospital discharges for CVD in the European population has increased by 26%, from 20.8 to 26.3/1000. This increase was more marked in eastern European countries and, to a lesser extent, in countries from the European Union (12 members, or the new enlarged EU, with 15 members). Over the same period, the number of hospital discharges for ischemic heart disease increased by 29% and for cerebrovascular disease by 41%.*

The Euro Heart Survey program collects data all over Europe in many cardiology fields (e.g., acute coronary syndrome [ACS], heart failure, percutaneous coronary intervention [PCI], revascularization, atrial fibrillation, valvular heart disease, congenital heart disease). Participation in the surveys is voluntary, and there are no financial incentives for the participating centers or investigators. Ideally, the Euro Heart Survey program would be representative of the whole of Europe, but it is clear that in many countries, only the best hospitals participate, with the result that the data may portray a more optimistic picture than reality. With each subsequent survey, the logistics have gradually been modernized and improved, moving from paper case report forms (CRFs) in the first surveys to electronic CRFs online, an online data collection system that provides each center with access to its own data, and comparisons to peer centers.

This chapter presents data collected in three consecutive surveys carried out in early 2000, 2004, and 2007. The first two surveys were done over a fixed period of time. The last survey is still underway and is being transformed into a permanent registry.

*These data are from the World Health Organization (WHO) European Health for All database (HFA-DB) http://data.euro.who.int/hfadb, the WHO Mortality database (WHOMDB) http://data.euro.who.int/dmdb, the Eurostat databases http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home, and the U.S. Census Bureau International database http://www.census.gov/ipc/www/idb.

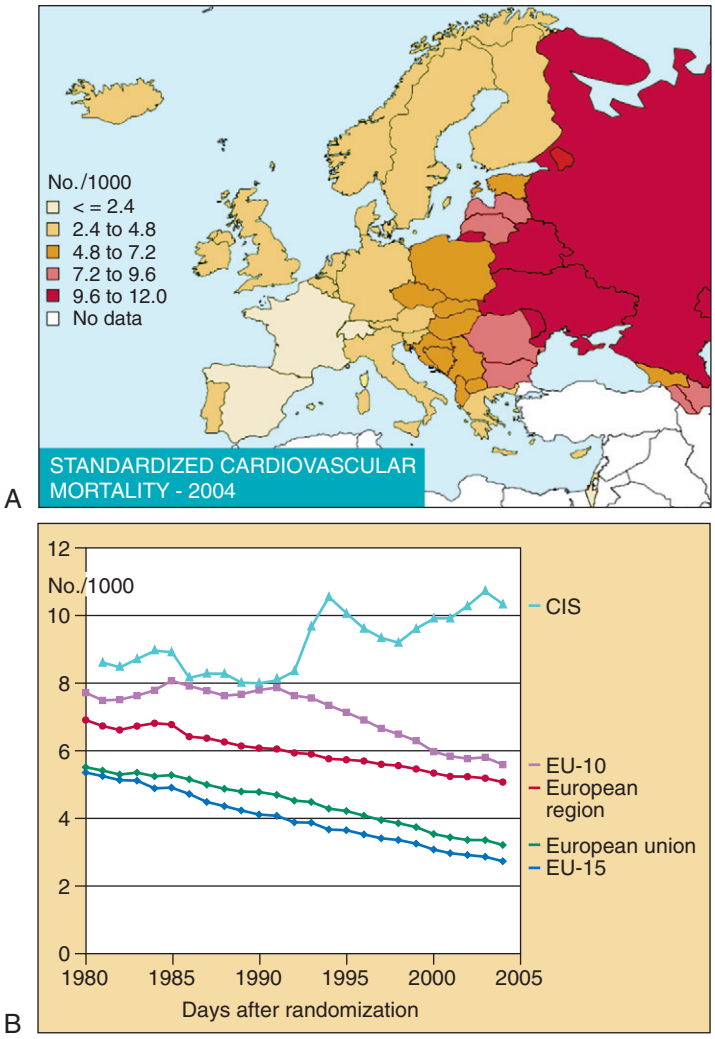

FIGURE 4–1 **A,** Standardized cardiovascular mortality among men in 2004. **B,** Evolution of mortality in men from cardiovascular disease in Europe from 1980 to 2005. CIS, 12 countries of the Commonwealth of Independent States (12 of 15 countries of the former Soviet Union—Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan); European Union (EU), 25 member states (Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom); EU-10, 10 member states that joined the EU from May 1, 2004 (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia); EU-15, 15 member states of the EU prior to May 1, 2004 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom); European Region: 52 member states of the WHO European Region.

EURO HEART SURVEYS: ACUTE CORONARY SYNDROMES I AND II

In 2000, the ESC encompassed 47 countries across Europe and the Mediterranean basin. To delineate the characteristics, treatments, and outcomes of ACS patients treated in representative ESC member countries, and particularly to examine the adherence to current practice guidelines, the ESC sponsored the large-scale Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS; EHS ACS-I), a prospective survey of 25 ESC member countries. The enrollment period was planned from September 4 to December 31, 2000, but it was extended to May 15, 2001, with data collection beginning in early 2001 in some countries.

During the study period, 14,271 patients were screened, of whom 10,484 were finally diagnosed with ACS. The initial diagnosis for these patients was ACS with ST elevation in 42.3%, ACS without ST elevation in 51.2%, and ACS with an undetermined electrocardiographic pattern in 6.5%. Altogether, 32.8% of patients had a final diagnosis of Q-wave acute myocardial infarction (AMI), 25.3% non–Q-wave AMI, and 41.9% unstable angina (UA).[4]

The patients were enrolled in 65 clusters (103 hospitals)—65% in academic hospitals, 77% in hospitals with catheterization laboratories, and 57% in hospitals with cardiac surgery facilities. The vast majority of patients with ST-elevation ACS were originally admitted to coronary care units or a general cardiology ward, with only a minority of patients admitted to internal medicine wards. ACS patients with other electrocardiographic patterns were more than twice as likely to be admitted to internal medicine wards. The median (25th, 75th percentiles) duration of hospitalization was 8 (5, 12) days for all patients, 8 (5, 12) for ST-elevation patients, 7 (4, 12) days for non–ST-elevation patients, and 8 days (5, 13) for patients with an undetermined electrocardiographic pattern. When analyzed based on the final diagnosis, the duration of hospitalization was 7 (4, 12) days for patients

with UA, 7 (5, 11) days for patients with non–Q-wave AMI, and 8 (5, 13) days for patients with Q-wave AMI.

Coronary angiography was performed in approximately half of the survey cohort during the initial hospitalization. PCIs were performed more commonly for patients with ST-elevation ACS.

Among patients with ST-elevation ACS, 55.8% received any form of reperfusion therapy, 20.7% received primary PCI, and 35.1% had fibrinolytic therapy. Among patients with ST-elevation ACS who underwent reperfusion therapy, the median time (25th, 75th percentiles) from symptom onset to arrival in the emergency room was 176 minutes (90, 465) and the median time from arrival to the emergency room to reperfusion therapy was 59 minutes (30, 109)—40 minutes (25, 70) to the initiation of fibrinolytic therapy and 93 minutes (60, 170) to the first balloon inflation. Among patients undergoing primary PCI in this subgroup, 45.4% received a platelet glycoprotein IIb/IIIa inhibitor and 70.7% received an intracoronary stent.

While in hospital, a substantial proportion (7% to 17%) of patients with ACS did not receive aspirin, especially if they had an initially undetermined electrocardiographic pattern (results are presented as ranges for the different forms of ACS). Unfractionated heparin was more commonly used among patients with ST-elevation ACS, whereas low-molecular-weight heparin (LMWH) was more commonly used in the other subgroups. Altogether, platelet glycoprotein IIb/IIIa inhibitors were not commonly used in this survey cohort (8.9% to 19.6% for the different types of ACS), and if they were used it was more common in the ST-elevation ACS group. Although β-adrenergic blockers were commonly used in all subgroups, their intravenous use was low, 5.9% to 13.5% for the different types of ACS).

A substantial proportion of patients did not receive aspirin at discharge (11.5% to 16.9% for the different types of ACS), only partially explained by the widespread use of anticoagulation agents or the other antiplatelet agents, ticlopidine and clopidogrel. Although β-adrenergic blockers were commonly prescribed (67.4% to 76.9% for the different types of ACS), the use of agents blocking the angiotensin axis was less common (55.7% to 64.1% for the different types of ACS). Over 50% of patients received lipid-lowering treatment with statins at discharge; most of them began receiving this treatment during the hospitalization.

Patients with ST-elevation ACS were more likely to undergo PCI in the interim between hospital discharge and the 30-day follow-up, whereas patients with non–ST-elevation ACS were more likely to undergo coronary bypass surgery.

In-hospital survival status was available for all patients, with a mean in-hospital death rate of 4.9% for the entire survey cohort. The in-hospital death rate for patients with ST-elevation ACS was 7.0%, for patients without ST-elevation ACS 2.4%, and for patients with an undetermined initial electrocardiographic pattern 11.8%. At 30 days, the death rates were 8.4%, 3.5%, and 13.3%, respectively (with 30-day survival status available for 90.7%, 88.8%, and 88.6%, respectively), resulting in a mean 30-day death rate for the entire cohort of 6.3%.

To examine the management and implementation of more contemporary guidelines, we conducted the second Euro Heart Survey of ACS during 2004 in 190 medical centers from 32 countries in Europe and the Mediterranean basin.[5] Of the 190 centers, 91 that participated in the survey were affiliated with academic institutions, 123 had catheterization laboratories, and 61 had cardiac surgery facilities. Of the patients who were hospitalized, 53% were in medical centers affiliated with academic institutions and 46% were hospitalized in tertiary care centers. Seventy-three percent of the patients were treated in hospitals that had on-site catheterization laboratories and 37% in centers that had facilities for cardiovascular surgery. Among the centers participating in EHS ACS-II were 34 centers that had also participated in the first Euro Heart Survey on ACS.

The EHS ACS-II cohort included 6385 patients with a final diagnosis of ACS. The proportion of patients with an initial diagnosis of ACS with ST elevation rose from 42% in EHS ACS-I to 47% in EHS ACS-II, whereas non–ST-elevation ACS patients comprised 51% of the ACS-I participants and 48% of those included in ACS-II. Five percent and 6.5% of the patients in ACS-II and ACS-I, respectively, presented with an undetermined electrocardiographic pattern.

Examination of the characteristics of all patients included in the first and second EHS surveys of ACS showed a considerable degree of similarity with respect to mean age (65.2 vs. 64.7 years in ACS-I vs. ACS-II), proportion of men (67.5% in ACS-I vs. 70.1% in ACS-II), and the proportion of patients with risk factors. Comparison of the characteristics of the patients in the 34 centers participating in both surveys showed much similarity in the two periods.

In the second survey, more patients were hospitalized in coronary care units (70% vs. 62.4%), whereas fewer were treated in cardiology wards (19.1% vs. 22%) and in internal medicine wards (7% vs. 13.8%). The proportion of patients hospitalized in other wards was 3.9% in ACS-II versus 1.8% in ACS-I.

Coronary angiography, PCIs, and intracoronary stents were used more frequently in ACS-II than in ACS-I, including primary PCI for ST-elevation ACS. The increase in the proportion of patients undergoing coronary angiography, PCIs, and stent implantation among those hospitalized in the 34 centers was higher than in the full ACS-I and ACS-II cohorts (from 60.5% to 82.3%, 45.9% to 69.9%, and 34.1% to 63.6% for patients with ST-elevation ACS, respectively, and from 54.3% to 72.1%, 27.3% to 46.7%, and 19.6% to 43.6% for non–ST-elevation patients, respectively). In addition, a greater proportion of patients received evidence-based medications during their hospitalization and at discharge in ACS-II compared with ACS-I, irrespective of their initial electrocardiographic diagnosis (Fig. 4-2).

Similarly, a comparison between the two surveys in terms of time delay showed a reduction in the median time (in minutes) from symptom onset to arrival at the emergency department, from 210 (105 to 625) in ACS-I to 170 (90 to 420) in ACS-II. This reduction was a result of decreases in both time from symptom onset to first call, from a median 120 (50 to 450) in ACS-I to 105 (40 to 306) in ACS-II, as well as time from first call to emergency room arrival, from a median 50 (26 to 91) in ACS-I to 42 (15 to 80) in ACS-II. A reduction in the length of stay in the reporting department was also observed, with a median stay of 8 days in EHS ACS-I to 7 days in EHS ACS-II. In the 34 centers that participated in both surveys, a reduction was also noted, from 8 to 6 days.

Among patients with ST-elevation ACS, 63.9% received primary reperfusion treatment compared with 56% in EHS ACS I (51.8% of reperfused patients were treated with primary PCI, 7% with facilitated PCI, and 41.2% with fibrinolytic therapy, with or without rescue interventions; Fig. 4-3). A total of 1084 patients presenting with ST-elevation ACS did not receive primary reperfusion therapy. The major reasons were late arrival (30.1%), uncertain diagnosis (11.2%), early resolution of ST-elevation ACS (11.6%), and contraindications (6.5%). Additional reasons given by the treating physician included advanced age, premature death, patient refusal, and lack of catheterization laboratory facilities.

Crude mortality in-hospital and at 30 days was lower in the total ACS-II cohort (Fig. 4-4) than the ACS-I cohort. The reduction in mortality from ACS-I to ACS-II was more marked in the 34 centers that participated in both surveys (from 5.6%

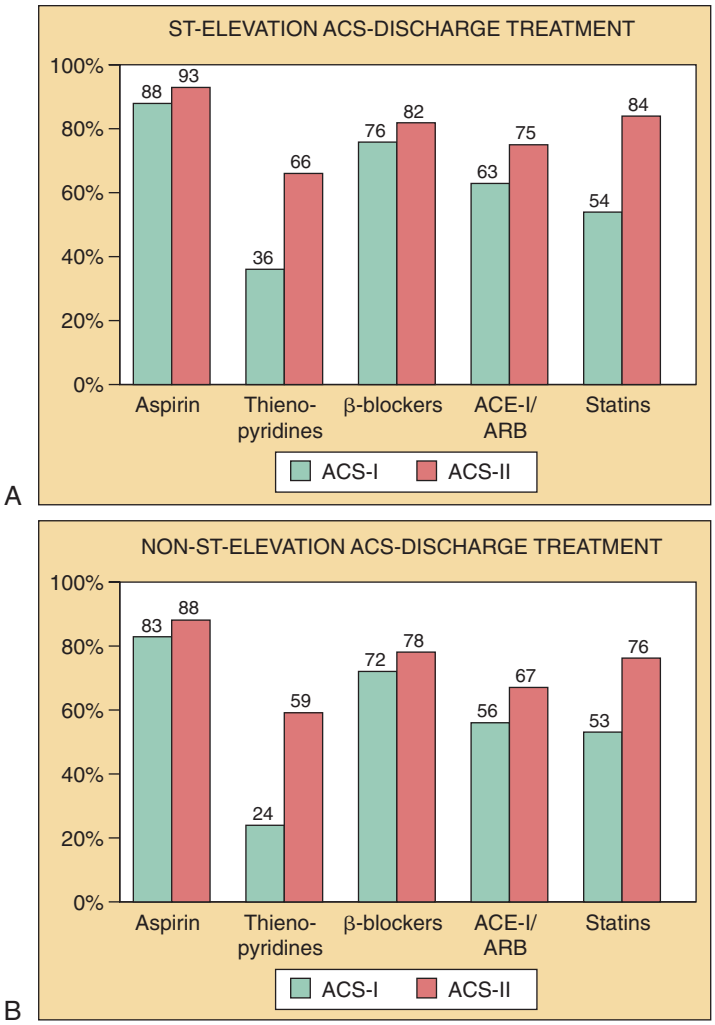

FIGURE 4–2 Comparison of treatment of ST-elevation MI patients **(A)** and non–ST-elevation MI patients **(B)** at discharge in ACS-I and ACS-II in 34 centers that participated in both surveys. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

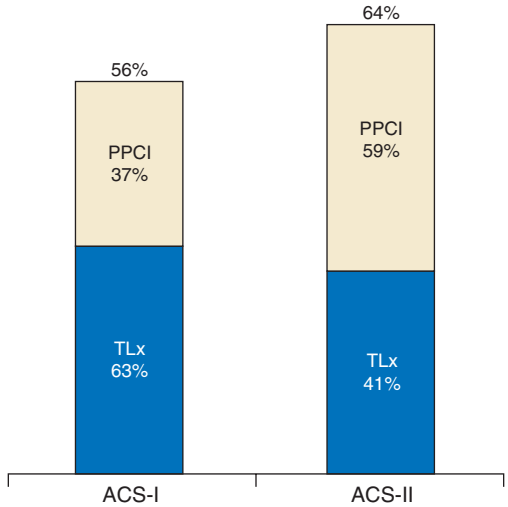

FIGURE 4–3 Comparison of the use of primary reperfusion therapy in ACS-I and ACS-II. PPCI, primary percutaneous coronary intervention; TLx, thrombolytic therapy.

to 4.4% and 6.8% to 5.6% for in-hospital and 30-day mortality, respectively). After adjustment in multivariable analysis for the 34 centers, the odds ratio (OR) for in-hospital mortality in ACS-II in comparison with ACS-I was 0.58 (95% confidence interval [CI], 0.40 to 0.83), and for 30-day mortality, 0.66 (95% CI, 0.48 to 0.92).

In the 34 centers that participated in both surveys, the increases in the use of evidence-based therapies and interventions were accompanied by an even greater reduction in mortality between ACS-I and ACS-II. The relative risks of hospital and 30-day mortality were 42% and 34% lower in ACS-II in comparison with ACS-I, although patient characteristics were similar. Therefore, the improved outcome in the second survey may be partially attributed to a significant increase in guideline adherence in these centers in ACS-II versus ACS-I.

These data show that over time, management of ACS has improved, as assessed by the two Euro Heart Surveys on ACS. It was also shown that the mere fact of participating in the survey led to an improvement in practice. The comparison of management in the 34 centers that participated in both surveys provides valuable evidence that better information about patient management and participation in surveys can improve management and outcome.

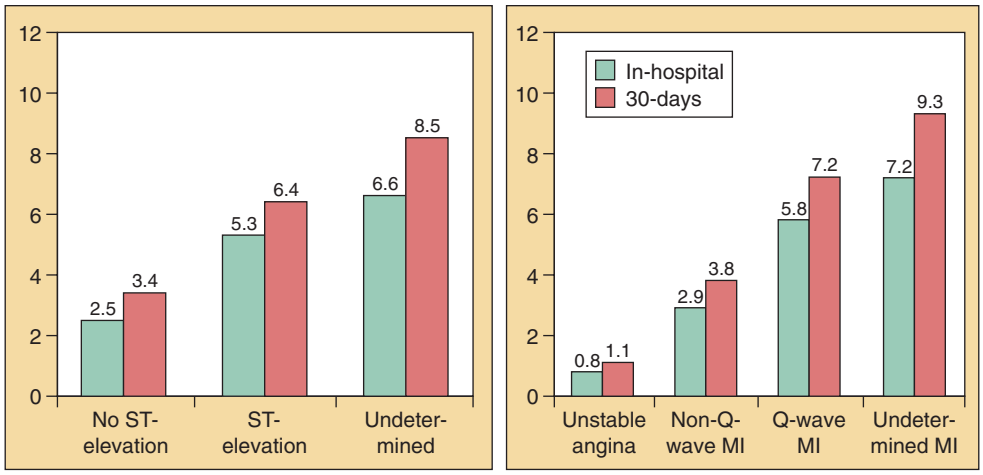

FIGURE 4–4 In-hospital and 30-day crude mortality by initial ECG presentation and final diagnosis in EHS-ACS II (data on 30-day mortality were missing for 283 patients, 4.4%).

MOVING TOWARD A PERMANENT REGISTRY: EURO HEART SURVEY ON ACUTE CORONARY SYNDROMES III

The European Society of Cardiology now brings together more than 45,000 cardiologists, scientists, and other professionals in cardiovascular disease management from 50 countries in Europe in its broadest geographic sense. As noted, considerable differences exist among these countries with respect to the structure of the population, socioeconomic development, and health care systems. The first two surveys showed that data collection on ACS patients and on those undergoing cardiac procedures is essential to improve the quality of patient care and the efficient use of resources in cardiology practice. In addition, the collection of data in the Euro Heart Survey program now uses the Cardiology Audit and Registration Data Standards (CARDS) for Europe, developed by the ESC in cooperation with the European Commission and endorsed by the governments of all European Union members, to guarantee consistency of definitions and data.[6]

The two ACS surveys, which collected data on ACS presentation, treatment, and outcomes in Europe in 2000 and 2004, showed a large variation in adherence to guidelines in clinical practice in different parts of Europe, as well as among the different centers within each country. On the other hand, the results of the two Euro Heart Surveys on ACS in 2000 and 2004 demonstrated an improvement of acute and long-term treatment, which was associated with a significant reduction of in-hospital and 30-day mortality. Based on these encouraging findings, the Euro Heart Survey program moved from its former cyclic survey structure to a continuous data collection in an ongoing ACS registry. The objective of this registry is to develop a quality assurance program (Fig. 4-5) and to carry out the following:

1. Document the current presentation of ACSs in Europe.
2. Determine the adherence to current ESC guidelines for the management of the different types of ACS with respect to acute reperfusion treatment (ST-segment elevation myocardial infarction), invasive versus conservative treatment (non–ST-segment elevation myocardial infarction ACS), and adjunctive medical treatment (all ACS).
3. Assess the immediate, in-hospital, and 1-year outcomes of ACS patients.
4. Assess the use of medical resources and its impact on outcomes in different countries and different types of hospitals.
5. Prospectively test the value of existing treatment algorithms to predict disease-related outcomes.
6. Compare current clinical practice of ACS in 2007 to 2008 with clinical practice in 2000 and 2004 (data from the Euro Heart Surveys ACS-I and ACS-II).

Data of consecutive patients with ACS are collected using online Internet data entries. The electronic case report form is provided by the Euro Heart Survey Team at the European Heart House based on CARDS.[6] During the ongoing ACS registry, the Euro Heart Survey Team at the European Heart House provides reports of all collected data, including patient characteristics, treatment, and clinical outcomes of the enrolled patients to every participating center on a regular basis. The data of the participating center will be compared with the data from its country and from the overall European data (see Fig. 4-5). No data from any participating center will be released to any other participating hospital or medical institution. This benchmarking system will offer the participating center a tool for internal quality assurance, aiming for better adherence to the ESC practice guidelines for the management of ACS. This concept of quality assurance by ongoing data registration is supported by data from the international GRACE-Registry.[7] In this registry, improvements in the management of patients with ACS resulting in significant reductions in the rates of new onset of heart failure and mortality and in rates of stroke and MI at 6 months were observed in centers participating in the registry on a permanent basis.

Quality assurance in medicine is a continuous process and involves many different components. The Euro Heart Survey program with its ACS registry continues to provide insights regarding clinical practice throughout Europe. The hope is that this will encourage participating hospitals to improve the quality of care further and to apply guideline-recommended diagnostic procedures and therapy more effectively, which will help reduce the burden of cardiovascular CVD in Europe in the future (Fig. 4-6).

CONCLUSIONS

The Euro Heart Survey program was launched by the European Society of Cardiology at the turn of the new century at the initiative of then-President Maarten Simoons. The aim was to obtain a comprehensive overview of CVD across Europe, in its largest geographic sense, to highlight the differences in incidence, management, access to resources, and outcomes. Over time, the Euro Heart Surveys were extended to a range of areas in the field of cardiology, covering acute

Euro Heart Survey

ACS Registry (2006–2007) benchmarking report
Medical history
Inclusion: ESC member countries
Exclusion: ---
Comparison: Test centre vs. own country vs. rest of Europe

Date: 23/11/2007
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	Total	Centre XY	Own country	Europe
Number of patients	3689	366 (9.9%)	780 (21.1%)	2543 (68.9%)
History of CAD				
History of previous Myocardial Infarction (MI)	23.4% (862/3676)	22.5% (82/365)	21.9% (171/780)	24.1% (609/2531)
Prior Angina	34% (1247/3664)	29.6% (108/365)	33.3% (260/780)	34.9% (879/2519)
Previous percutaneous coronary intervention	13.0% (478/3683)	16.1% (59/366)	18.8% (147/780)	10.7% (272/2537)
Coronary Artery Bypass Graft (CABG)	5.3% (197/3685)	5.7% (21/366)	4.5% (35/780)	5.6% (141/2539)
History of Congestive Heart Failure (CHF)	10.7% (392/3667)	10.1% (37/366)	5.1% (40/779)	12.5% (315/2522)
History of stroke	6.6% (244/3682)	10.7% (39/366)	5.4% (42/780)	6.4% (163/2536)
History of peripheral vascular disease	9.3% (343/3677)	12.6% (46/366)	6.3% (49/779)	9.8% (248/2532)
History of chronic renal failure	5.9% (216/3674)	8.2% (30/365)	5.9% (46/780)	5.5% (140/2529)
Chronic lung disease	8.3% (304/3680)	10.1% (37/365)	8.3% (65/780)	8.0% (202/2535)
Risk factors				
Family history of CAD	27.0% (918/3400)	22.8% (81/355)	10.6% (79/745)	33.0% (758/2300)
Current smoker	31.7% (1154/3637)	29.8% (109/366)	29.1% (225/772)	32.8% (820/2499)
Current/former smoker	58.5% (2129/3637)	64.2% (235/366)	57.4% (443/772)	58.1% (1451/2499)
Diabetes mellitus	25.9% (944/3639)	28.1% (103/366)	29.5% (229/777)	24.5% (612/2496)
Diet alone	14.9% (141/944)	21.4% (22/103)	10.5% (24/229)	15.5% (95/612)
Insulin	24.9% (235/944)	30.1% (31/103)	32.8% (75/229)	21.1% (129/612)
Oral agent	59.6% (563/944)	48.5% (50/103)	58.5% (134/229)	61.9% (379/612)
Newly diagnosed	4.8% (45/944)	4.9% (5/103)	2.2% (5/229)	5.7% (35/612)
History of hypertension	63.7% (2317/3639)	59.3% (217/365)	61.4% (478/779)	65.0% (1622/2494)
History of hypercholesterolaemia	50.0% (1658/3314)	56.2% (204/363)	50.1% (388/774)	49.0% (1066/2177)

Percentages and numbers or
Medians and quariles or
Mean and standard deviation are given

©ESC, Euro Heart Survey Programme
Analysis provided by IHF, Ludwigshafen, Germany

Dr. M. Hochadel
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FIGURE 4–5 Benchmark report of the ACS registry in the Euro Heart Survey Programme. Data from the participating center is compared with data from the other participating centers in its country and with data from the other participating centers in Europe.

coronary syndromes, percutaneous coronary intervention, heart failure, atrial fibrillation, revascularization, and congenital heart disease, and valvular heart diseases, among others. All these diseases represent a major burden to the European population and their health care systems. Euro Heart Survey data have made it possible to raise awareness among politicians and decision makers about the need for further investment and research in CVD, as well as investment in its management and prevention. In this regard, the ESC has been successful in alerting the European Commission to the problem of CVD in Europe, and this partnership has given rise to a European charter for the prevention and management of CVD in Europe (for further information, see www.heartcharter.eu). Another major achievement has been to raise awareness among European cardiologists about the management of CVD and the need to adhere to clinical practice guidelines. It was clearly shown over the course of successive surveys that clinician adherence to guidelines improved over time. The mere fact of participating in the surveys encouraged physicians to improve patient management. Data from centers that participated in both ACS surveys showed that this improvement in adherence to guidelines led to better outcomes for patients. In this sense, the objectives of the Euro Heart Survey were achieved, both from medical and health care perspectives.

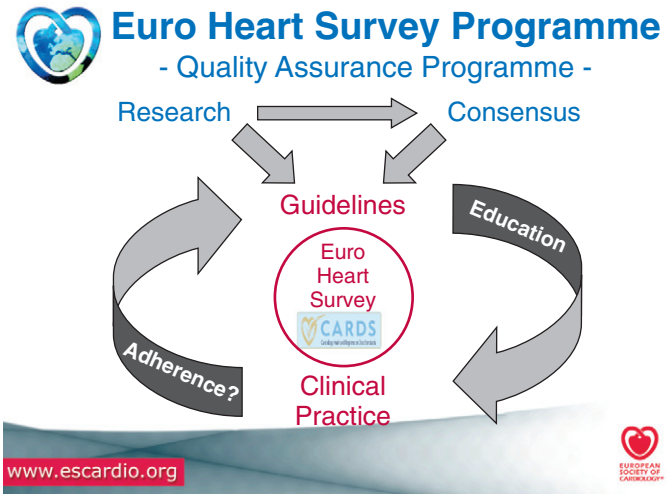

FIGURE 4–6 The Euro Heart Survey Programme as European quality assurance of cardiac care for the improvement of guideline adherence. *(From European Society of Cardiology (ESC). Euro Heart Survey (EHS). Available at www.escardio.org.)*

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CHAPTER 5

Acute Coronary Syndrome in North America

Nipun Arora, Ralph G. Brindis, and Christopher P. Cannon

A large number of patients with acute coronary syndrome (ACS) are not given therapies that can save lives and prevent recurrent cardiac events. Analyses of trends over the last decade from the U.S. National Registry of Myocardial Infarction (NRMI) have shown a 23% reduction in risk of hospital mortality from acute myocardial infarction.[1-3] This change has occurred because of aggressive risk factor modification and improvement in pharmacologic and interventional treatments.[4,5] However, despite clear evidence about the proven benefits of these therapies, there is concern regarding suboptimal adherence to guideline recommendations in clinical practice. Thus, significant efforts are being made currently to monitor the quality of care and adherence to evidence-based guidelines in patients with ACS to improve clinical outcomes. This chapter will review the current prevalence of ACS in North America, gaps in treatment, and initiatives to improve safety and outcomes in these patients by the development of large national registries.

According to the American Heart Association (AHA) statistics, 1.4 million patients in the United States are hospitalized annually for ACS.[1,6] From 1990 to 2006, of all patients with acute myocardial infarction (AMI), the proportion with non–ST-segment elevation myocardial infarction (NSTEMI) increased exponentially from 14.2% to 59.1% (Fig. 5-1).[3] Possible explanations for this include adoption of serum troponin as a sensitive biomarker for diagnosing AMI in the mid- to late 1990s, increased use of medical therapy, and coronary revascularization, measures that could have led to early detection of AMI and prevented the transition from NSTEMI to ST-segment elevation myocardial infarction (STEMI) in some patients. There has also been a change in the demographics of patients with ACS. Clinicians are now faced more frequently with higher risk patients of increasing age and with multiple comorbidities, including heart failure, stroke, diabetes, hypertension, and previous coronary revascularization.[7-9] Over the last decade, the mean age of presentation with AMI has risen from 65.3 to 68.0 years, and the proportion of women has increased from 35.3% to 39.3%.

Morbidity and mortality after ACS remain substantial. Within the next 5 years, recurrent myocardial infarction will occur in up to 32% of patients, heart failure in 29%, stroke in 17%, and sudden cardiac death in 1% to 15%.[1,10] The African American population has the highest risk for these events. Events also tend to occur more commonly in women and older adults.[3]

In randomized clinical trials (RCTs), the in-hospital mortality rates have been reported to be approximately 2% from NSTEMI and from 3% to 5% in patients with STEMI.[11-14] Interestingly, however, clinical registries report higher rates of in-hospital mortality, approximately 5% to 7% for NSTEMI and 7% to 9% for STEMI.[15-17] This discrepancy is likely related to the delivery of better medical care and exclusion of higher risk patients in RCTs. Long-term mortality, conversely, is higher in patients with NSTEMI than in those with STEMI. This is related to a higher risk patient profile, including frequent multivessel disease, more jeopardized myocardium, and a greater concurrent risk of both recurrent ischemia and reinfarction in those with NSTEMI.[18]

GAPS IN ACUTE CORONARY SYNDROME TREATMENT

Recent studies have documented substantial gaps between evidence-based recommendations and clinical management of patients with ACS. A disturbing trend has been noticed in the analyses of various clinical registries, suggesting that the highest risk patients with ACS are paradoxically treated less aggressively.[19-24] Treatment patterns from the NRMI registry that included more than 1.9 million patients showed a 24% risk reduction in early mortality from STEMI and a 23% reduction in early mortality from NSTEMI by practicing evidence-based therapies.[3] Similarly, a recent registry of patients with non–ST-segment elevation (NSTE) ACS treated at 350 U.S. hospitals has found that adherence to American College of Cardiology (ACC)–AHA guidelines led to a reduction in absolute in-hospital mortality from 6.3% to 4.1%.[5] However, despite these benefits, up to 25%

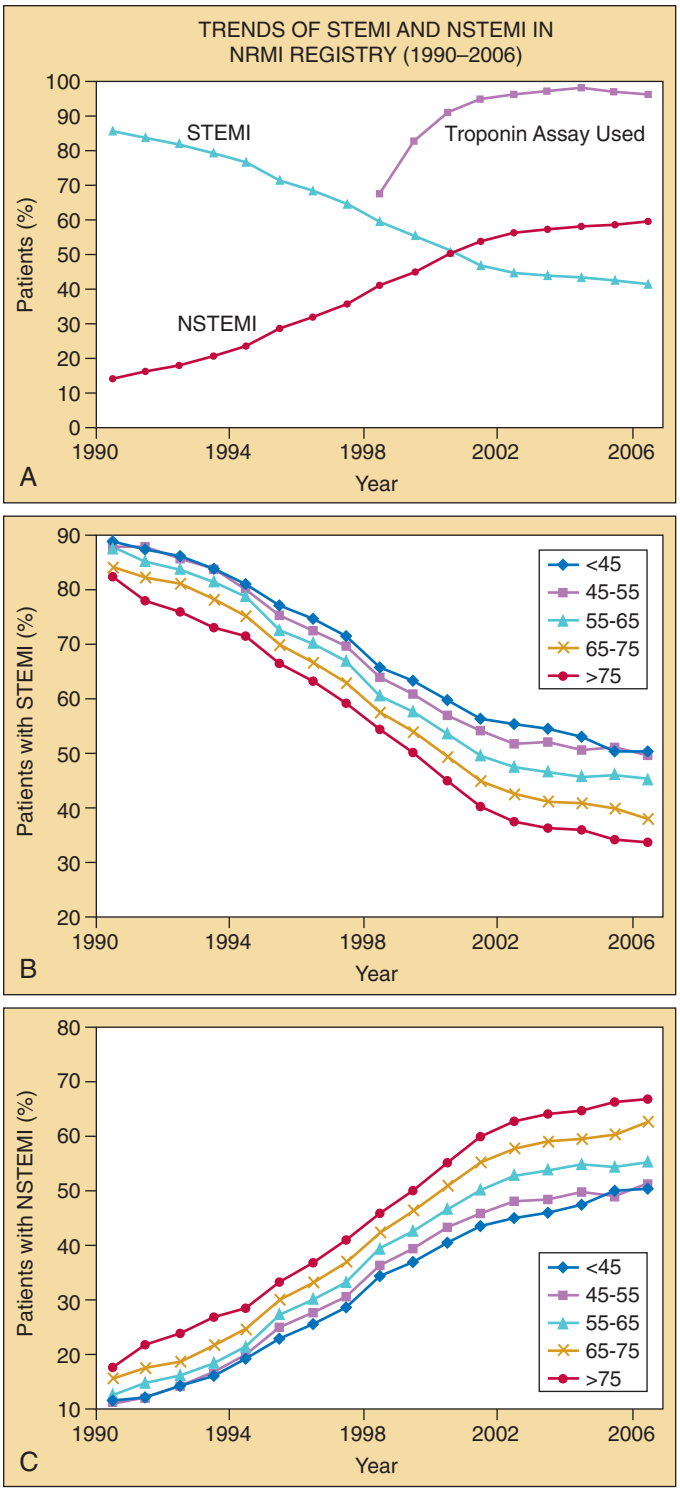


FIGURE 5–1 Trends of STEMI and NSTEMI in NRMI Registry (1990-2006). **A,** Proportion of patients in NRMI-1 to NRMI-5 classified as having STEMI or NSTEMI, and proportion of patients in whom troponin assay was used to diagnose AMI. **B** and **C,** Proportion of patients with STEMI and NSTEMI, respectively, stratified by age (years; $P = .0001$ for all).

of opportunities to provide the guideline-recommended care were missed in these patients.[5,25]

To ensure that patients with ACS benefit from these proven therapies, the ACC-AHA have published evidence-based treatment guidelines that provide a consensus—or standard of care—for the diagnostic or therapeutic interventions appropriate for most patients in most circumstances.[26-28] These guidelines also provide a method for measuring the quality of cardiovascular care provided by individual institutions, or performance measurement.[29] These performance measures have been used to determine hospital referral patterns, public reporting, reimbursement, and maintaining institutional accreditation.[30-32]

REAL-WORLD ACUTE CORONARY SYNDROME REGISTRIES IN NORTH AMERICA

Although most clinical practice guidelines in cardiology are based on information obtained from RCTs, guideline writers are sometimes hampered by not having enough information about the real-world practice patterns at a given time. Recently, several registries have been created in the United States and globally to collect information regarding treatment of ACS patients (Table 5-1). These registries function complementary to RCTs by providing information about real-world patients who are generally higher risk and may have been excluded in the RCTs.[33]

Some of the largest national ACS registries in the United States include the NRMI, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC and AHA Guidelines (CRUSADE), and Get With The Guidelines (GWTG). In addition to providing a large national databank to collect information on patients with ACS, these registries act as important benchmarking tools to compare performance of various hospitals by reflecting adherence to guideline-recommended therapies.[34]

Several other local and regional registries have played an important role in improving guideline adherence for the management of ACS, including the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) at the University of California at Los Angeles Medical Center, and the ACC-sponsored pilot project, Guidelines Applied in Practice (GAP).[35] These projects have shown that mere publication of evidence-based guidelines does not guarantee their dissemination, acceptance, or use for patient care. There are many missed opportunities for the treatment of high-risk patients, and treatment disparities persist.

To improve the quality of care of ACS patients further, the NCDR (National Cardiovascular Data Registry)-ACTION was created in 2007 by combining two previously existing national ACS registries, NRMI and CRUSADE. The ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry is the largest, most comprehensive national ACS database and quality improvement initiative developed in the United States, enabling hospitals to measure their performance in treating patients with ACS against national benchmarks.[36] With more than 150,000 patient records and 350 hospitals participating, the main objective of the ACTION registry is to assess and report treatment patterns and outcomes of STEMI and NSTEMI patients in the United States. ACTION also merged recently with AHA's GWTG program, which began in 2009 as the ACTION Registry-GWTG.

CHAMP (Cardiac Hospitalization Atherosclerosis Management Program)

The first quality initiative to improve clinical outcomes in patients with acute myocardial infarction was the CHAMP.[37] This was designed and implemented at the University of California Los Angeles (UCLA) Medical Center. CHAMP

TABLE 5–1 Acute Coronary Syndrome Registries in North America

Registry	Centers Included	Timeline	Design	Type of Registry	Outcomes
CHAMP (Cardiac Hospitalization Atherosclerosis Management Program)	Single center, at UCLA	1994-1995	Initiate pharmacologic therapy and lifestyle modification during hospital admission	ACS and ischemic heart failure, 302 patients and 256 controls	Increased use of aspirin, beta blockers, ACE inhibitors, and statins at discharge; reduction in 1-yr mortality (7.0% vs. 3.3%) and AMI (7.8% vs. 3.1%)
GWTG (Get With the Guidelines)	Nationwide, multicenter, AHA initiative	2000-2001 (pilot project) 2000-2009 (national initiative)	Internet-based tool to improve management, compliance; used teachable moment concept	AMI; 1738 Pilot National-CAD >250,000	Improved adherence to pharmacologic therapy and smoking cessation for secondary prevention of CAD
GAP (Guidelines Applied in Practice)	10 health systems in Michigan	1998-2000	Improve guideline adherence by providing toolkit of standard orders and forms	AMI; ≈400 Medicare patients	Decreased 1-yr mortality with use of GAP tool-kit
NRMI (National Registry of Myocardial Infarction)	Nationwide, 1600 hospitals	1990-2006	Voluntary reporting of ACS presentation and treatment patterns	AMI; >2.5 million patients enrolled	Showed 23% reduction in early mortality from AMI over last 16 yr
CRUSADE (Can Rapid Risk Stratification of Unstable Angina Suppress Adverse Outcomes with Early Implementation of ACC-AHA Guidelines)	Nationwide, 400 centers	2001-2006	Track adherence to ACC-AHA guidelines for early management of ACS and treatment at discharge	ACS (mostly NSTEMI); >200,000 patients	10% decrease in mortality with every 10% increase in guideline adherence
NCDR-ACTION (National Cardiovascular Data Registry–Acute Coronary Treatment and Intervention Outcomes Network)	Nationwide; combined CRUSADE and NRMI into one registry	2007-2009	Comprehensive and nationwide assessment of NSTEMI and STEMI care	ACS; enrollment ongoing	
ACTION Registry-GWTG	Nationwide; combined ACTION and GWTG registries	2009-current	National registry to assess quality of care and outcomes in ACS patients	ACS; enrollment ongoing	

focused on the initiation of aspirin, statins titrated to achieve a low-density lipoprotein (LDL) cholesterol level less than 100 mg/dL, and beta blocker and angiotensin-converting enzyme (ACE) inhibitor therapy in conjunction with diet and exercise counseling before hospital discharge in patients with established coronary artery disease, including patients with ACS, ischemic heart failure, and those who underwent cardiac procedures (e.g., catheterization, angioplasty and/or stent placement, and coronary bypass).[38] This treatment program was based on the hypothesis that the initiation of therapy in the hospital setting would result in higher utilization rates both at the time of discharge and during longer term follow-up. Implementation of this program involved the use of a focused treatment guideline, standardized admission orders, educational lectures by local innovative thinkers, and tracking and reporting of treatment rates.

The CHAMP initiative achieved a significant increase in the use of lifesaving drugs. Before and after CHAMP, aspirin use in patients at discharge improved from 78% to 92% of patients ($P < .01$), beta blocker use improved from 12% to 62% ($P < .01$), ACE inhibitor use increased from 4% to 56% ($P < .01$), and statin use increased from 6% to 86% ($P < .01$; Table 5-2) The improvement in drug use was associated with improved clinical outcomes, as reflected in significant reductions in recurrent myocardial infarction and 1-year mortality rates in the post-CHAMP versus pre-CHAMP era (7.8% vs. 3.1%, and 7.0% vs 3.3%, respectively; $P < .05$ for both comparisons).[37] CHAMP was the first initiative to demonstrate that a systems approach to quality improvement could not only increase the use of guideline-recommended therapies, but also reduce the risk of recurrent events.

TABLE 5–2 Cardiac Hospitalization Atherosclerosis Management Program (CHAMP): Effects of Therapy (%)

	Pre-CHAMP		Post-CHAMP	
Therapy	At Discharge	1 Yr Postdischarge	At Discharge	1 Yr Postdischarge
Aspirin	78	68	92	94
Beta blocker	12	18	61	57
Nitrates	62	42	34	18
Calcium blocker	68	58	12	6
ACE inhibitor	4	16	56	48
Statin	6	10	86	91

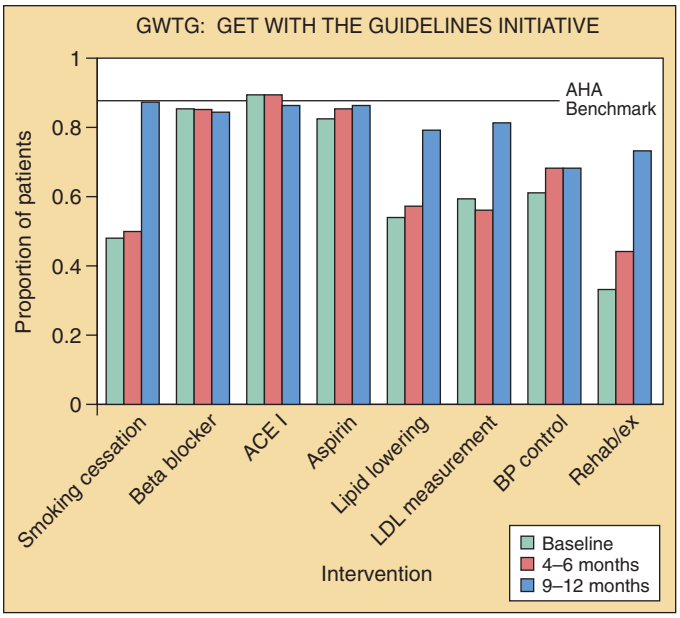


FIGURE 5–2 GWTG—Get With The Guidelines initiative.

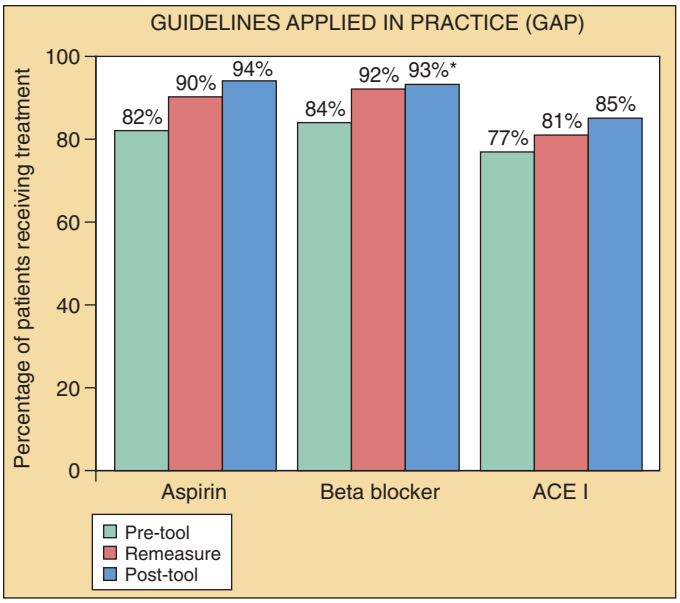


FIGURE 5–3 Guidelines Applied in Practice (GAP).

GWTG (Get With the Guidelines)

The success of CHAMP subsequently led to a national hospital-based quality improvement AHA initiative known as GWTG.[39] The focus of this program was to ensure treatment compliance in AMI patients before discharge. It was founded on the ACC-AHA guidelines for secondary prevention of cardiovascular diseases, and was designed to help health care providers treat patients consistently in accordance with these accepted guidelines. GWTG enrolled over 600 hospitals, and has a database of >250,000 hospitalized patients with CAD. It uses an Internet-based data management system that facilitates analysis of the care of patients with coronary artery disease (CAD) while they are in hospital, as well as hospital performance with regard to guideline adherence.[40] In addition to collecting data prospectively and measuring performance, the Internet-based patient management tool has incorporated reminder screens to provide immediate reference to the relevant guideline and alerts if measurements or interventions have been omitted.

During the first pilot year of GWTG, the rates of use of aspirin, beta blockers, and ACE inhibitors at discharge remained at 82% to 90% of eligible patients, the use of lipid-lowering therapy at discharge rose from 54% to 78% of patients, and smoking cessation counseling rose from 48% to 81% of patients (Fig. 5-2).[40] Since then, the program has been expanded nationally and has proved to be a sustainable and effective continuous quality improvement program that takes advantage of the teachable moment immediately after an acute event, when the patient is most likely to heed the advice of the health care provider.

As a result of the GWTG Internet tool, improvements have been seen in approaches to secondary prevention, including smoking cessation, aspirin use, statin use, LDL cholesterol measurement, blood pressure control, and cardiac rehabilitation.[41] The 10-year goal of the AHA was a 25% reduction in coronary heart disease, stroke, and risk (by 2010) by focusing on the treatment of acute event and secondary prevention. The GWTG program currently is addressing the prevention aspect, which, it is estimated, will account for 8% to 16% of the 25% goal.[40]

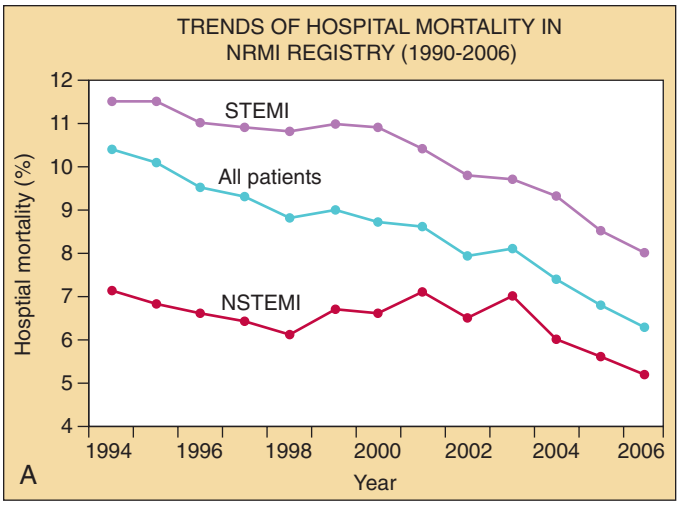
GAP (Guidelines Applied in Practice)

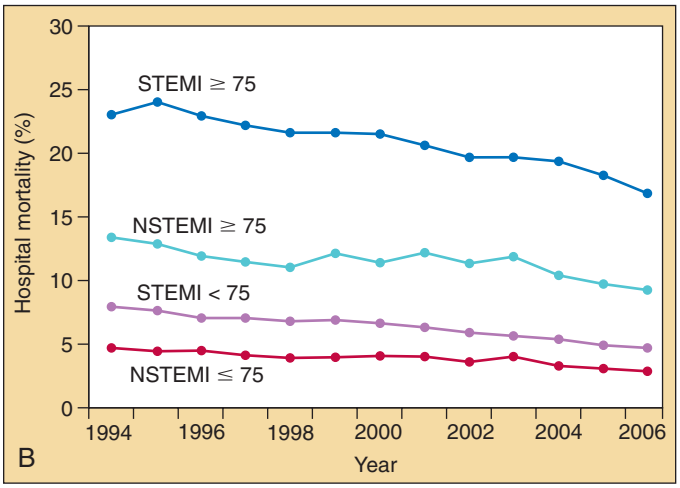
Further demonstration that continuous quality improvement can be implemented across a variety of institutions, patients, and caregivers has been provided by the GAP quality improvement project.[42] This project initially involved 10 health systems in Michigan, and was designed to improve guideline adherence in patients with AMI by bringing the ACC-AHA practice guidelines to the point of care. Participating hospitals used a customized tool kit that included standard orders for AMI, clinical pathway pocket guides or pocket cards, patient information forms, patient discharge forms, chart stickers, and hospital performance charts.[43]

The GAP project had a rapid timeline (1 year) and, during this period, it achieved significant increases in the use of aspirin (from 82% to 94% of patients; $P < .001$), beta blockers (from 84% to 93%; $P < 0.001$) on admission; and smoking cessation counseling (from 51% to 86%; $P < .001$) at discharge (Fig. 5-3). Importantly, GAP showed that these improvements in outcomes and compliance to guidelines were greater in patients who had use of the customized tools, including standard admission orders and patient discharge contracts.[35,44] Recent results from GAP have also shown a reduction in 1-year mortality with increased hospital use of the standard discharge contract in Medicare patient populations with AMI.[45]

NRMI (National Registry of Myocardial Infarction)

NRMI is one of the oldest and largest registries of AMI in the United States.[7,46] It was primarily developed as a means of providing clinicians with feedback on the quality of care provided to patients with AMI relative to their peers and promoting continuous improvement. It involved voluntary participation of 1600 hospitals, and more than 2.2 million patients have been followed. NRMI had five cohorts, in which the data collection survey evolved to reflect temporal changes in AMI care, including NRMI 1 (1990-1994), NRMI 2 (1994-1998), NRMI 3 (1998-2000), NRMI 4 (2000-2004), and NRMI 5 (2004-2006).





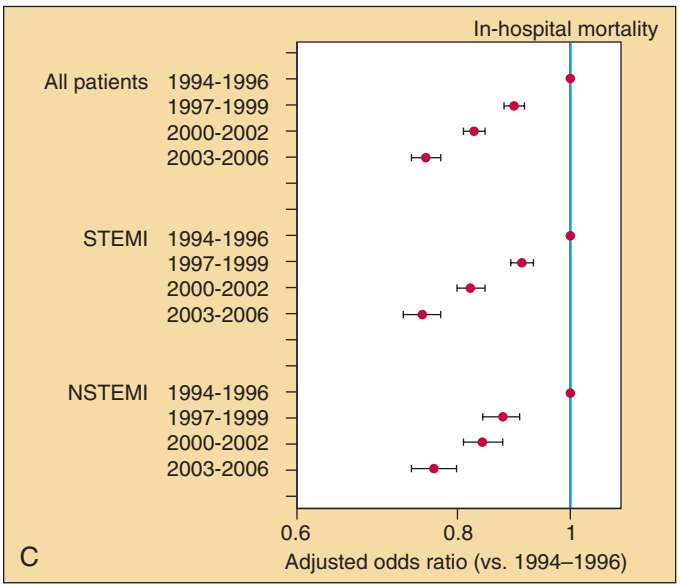


FIGURE 5–4 Trends of hospital mortality in NRMI Registry (1990-2006). **A,** Hospital mortality for all patients and those classified as STEMI or NSTEMI. **B,** Hospital mortality in patients younger than 75 and 75 years or older. **C,** Probability (OR; 95% CI) of hospital mortality by time after adjustment for baseline covariates (1994-1996).

Trends from NRMI registry have shown that the overall AMI care in the United States has improved over the last few years.[46] Since 1990 to 2006, improvements in acute therapies have likely accounted for up to 23% of the annual decline in risk for in-hospital AMI mortality (Fig. 5-4).[7] The use of acute guideline-recommended therapies administered increased significantly for patients with STEMI and NSTEMI, but still remained below 90% for most therapies (Fig. 5-5A).[47] Cardiac catheterization and percutaneous coronary intervention use increased in patients with STEMI and NSTEMI, whereas coronary bypass surgery use declined in both groups. Mortality for primary percutaneous intervention (PCI) decreased from 7.8% to 4.4% (see Fig. 5-5B).

However, despite overall care improvements, there were a number of eligible patients not receiving lifesaving therapies and disparities in care for key undertreated subgroups did not change.[46] Women, blacks, and patients 75 years or older were significantly less likely to receive revascularization or discharge lipid-lowering therapy relative to their counterparts.[47] NRMI also showed that despite national initiatives to measure and reduce door-to-balloon (DTB) times, guideline recommendations were met less than half the time.[48,49]

CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC and AHA Guidelines)

CRUSADE was developed as a U.S. national registry for NSTE ACSs to track the use of guideline-based acute and discharge treatments for hospitalized patients, as well as outcomes associated with the use of these treatments.[50] Care for more than 200,000 patients with NSTEMI, and later in more than 8800 patients with STEMI, at more than 400 high-volume acute care hospitals in the United States was tracked in CRUSADE from July 2001 to December 2006.[36]

The patient population included consecutive patients with ischemic symptoms within 24 hours of presentation lasting 10 minutes and high-risk features such as ischemic ST-segment electrocardiographic changes (ST depression, 0.5 mm; transient ST elevation, 0.5 to 1.0 mm, lasting less than 10 minutes) and/or cardiac biomarkers (troponin I or T and/or creatine kinase isoenzyme [CK-MB]) higher than normal upper limit within 24 hours of hospital admission. This large registry offered a unique opportunity to evaluate the use of risk stratification tools, recommended medications, clinical outcomes, and quality improvement interventions.[6,19,36] It also provided feedback to participating physicians and hospitals regarding their performance over time and compared with similar institutions.[5] Such access to data proved important in stimulating improvements in NSTE acute coronary syndrome care at participating hospitals for delivery of acute and discharge guideline-based therapy, as well as improving outcomes for patients. CRUSADE highlighted important lessons, including errors of omission (i.e., failure to use therapies proven to be beneficial), and errors of commission (i.e., inappropriate or incorrect use of treatment strategies, dose, procedures in patients with NSTE ACS.[51]

NCDR-ACTION (National Cardiovascular Data Registry–Acute Coronary Treatment and Intervention Outcomes Network)

The success of CRUSADE in improving patient care and publishing research attracted national attention from the Joint Commission, private payers, Medicare, and specialty groups such as the ACC. The NCDR decided to combine several quality improvement (QI) initiatives, including CRUSADE and NRMI, to launch a new initiative to improve the safety and outcomes for patients with ACS through the development of the NCDR-ACTION registry. Beginning in January

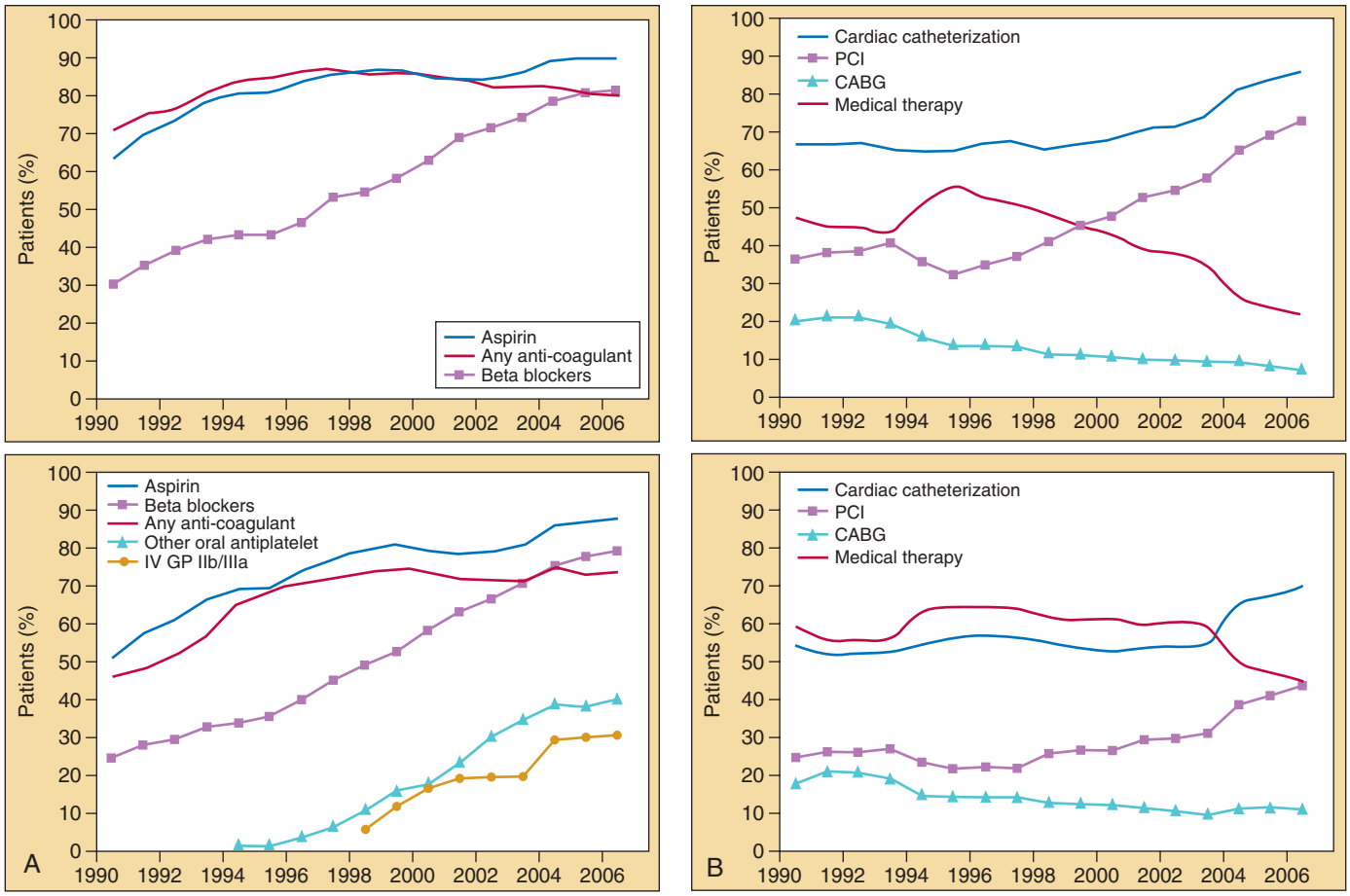


FIGURE 5–5 Temporal trends in medical therapies administered within 24 hours of admission in NRMI patients. **A,** Patients presenting with STEMI (*upper panel*) and with NSTEMI (*lower panel*). (Other oral antiplatelets and GP IIb/IIIa recorded in NRMI after 1994 and 1998, respectively.) **B,** Trends in procedural interventions in patients with AMI (STEMI, *upper panel;* NSTEMI, *lower panel*) (1990-2006).

2007, this initiative has combined the data collection and quality reporting features of these two leading national ACS registries to create a larger and more comprehensive cardiovascular patient database of both STEMI and NSTEMI.

Inclusion criteria included patients presenting with acute ischemic symptoms within the previous 24 hours, typically reflected by a primary diagnosis of STEMI or NSTEMI. Patients admitted for other clinical conditions who subsequently developed the first onset of ischemic symptoms, together with persistent ST-segment elevation and/or positive cardiac markers, later during their hospitalization were excluded.

The NCDR-ACTION registry aims to establish a national approach through the enrollment of most U.S. hospitals to improve the understanding of STEMI and NSTEMI treatment patterns, clinical outcomes, drug safety, and overall quality of care provided for patients with ACS through a registry that will provide direct feedback to physicians and institutions pioneered through the CRUSADE QI initiative.

Lessons Learned From Acute Coronary Syndrome Registries In North America

Underusage of Recommended Medical Therapy

For reasons not fully understood, certain high-risk patients presenting with AMI tend to be undertreated with evidence-based therapy when compared with lower risk patients. These include older patients, diabetics, women, African Americans, patients with renal insufficiency, and heart failure patients.[52,53] Because adherence to guidelines improves outcomes, and because high-risk patients have a higher mortality, these patients should receive therapy that most closely matches the guidelines. The opposite, however, happens in practice.

In the NRMI-4 registry, among all patients with NSTEMI who were eligible for glycoprotein (GP) IIb/IIIa inhibitors, only 25% received the therapy.[10] Analysis of the CRUSADE data showed that patients older than 75 years presenting with AMI received significantly less aspirin, beta blockers, and statins at discharge, and were less likely to have their lipid levels tested.[54,55] GP IIb/IIIa inhibitors in the CRUSADE data were also much less commonly used in older patients.[56] Similar disparities exist for African Americans when compared with whites, and for women when compared with men.[21,52,53] Although women have a greater incidence of death, recurrent AMI, and heart failure after AMI, they are treated less often in accordance to the ACC-AHA guidelines than men. They are also less likely to receive angiography, percutaneous coronary intervention, bypass surgery, and GP IIb/IIIa inhibitors.[57,58]

Patients with chronic kidney disease usually have multiple comorbidities such as diabetes, hypertension, coronary artery disease, and heart failure. These patients have high mortality associated with ACS, and most of the randomized trials have failed to study these patients. CRUSADE showed that despite the high-risk features in patients with chronic kidney disease, they were less likely to receive antiplatelet and antithrombotic therapies and much less likely to receive

cardiac catheterization and revascularization. Even simple and harmless interventions, such as smoking cessation counseling, dietary modification, and referral to cardiac rehabilitation facilities, were underused among these patients.[59]

Diabetes, heart failure, and mildly increased troponin levels are all well-established poor prognostic indicators that are paradoxically associated with a lower adherence to the management guidelines.[60,61] Similarly, although patients who have NSTEMI have higher long-term mortality when compared with STEMI patients and thus deserve equal or better secondary preventive measures, they are actually less likely than STEMI patients to receive aspirin, beta blockers, ACE inhibitors, lipid-lowering agents, smoking cessation counseling, and cardiac rehabilitation referral.[6,62]

CRUSADE also showed that lack of insurance and care by noncardiologists were strong predictors of underusage of guideline-recommended therapies and adverse outcomes.[63]

Delay in Treatment of STEMI Patients

Shorter time from symptom onset to reperfusion in STEMI consistently correlates with lower mortality for patients treated with fibrinolytic therapy and PCI. The ACC-AHA have recommended a time to fibrinolysis of less than 30 minutes and time to PCI of less than 90 minutes.[27] The current figures, however, are far from meeting the guidelines.[64] Analysis of NRMI-3 and NRMI-4 has shown that between 1999 and 2002, only 46% of STEMI patients receiving fibrinolytic therapy were treated within 30 minutes, and only 35% of patients treated with primary PCI were treated within 90 minutes.[48]

A recent analysis was reported from CRUSADE ($N = 2111$, January to December 2006) and ACTION patients ($N = 2013$, January to March 2007) with STEMI. The rate of primary PCI among STEMI patients without a listed contraindication to reperfusion in CRUSADE ($N = 2111$) was 80.3% versus 75.4% in similar STEMI patients ($N = 2013$) in ACTION. There was a progressive reduction in median DTB times for primary PCI, as well as more patients with DTB times 90 minutes or more over time. However, even in the most recent quarter, only two thirds of nontransferred primary PCI patients had DTB times of 90 minutes or less. These findings suggest that national initiatives such as the D2B Alliance are having an impact on DTB times. However, these data also highlight the needs that remain for ongoing quality assessment and improvement.[65]

Safety Concerns in Acute Coronary Syndrome Management

Increased attention has been paid to bleeding complications in patients with ACS, because bleeding increases the cost of hospitalization and has been associated with up to a threefold higher mortality.[66-69] CRUSADE highlighted the issue of overdosing with unfractionated heparin, low-molecular-weight heparin, and GP IIb/IIIa inhibitors in ACS patients (Fig. 5-6). The results indicated that 42% of patients with NSTE ACS receive one initial dose or more outside the recommended range.[55] An excess dose of unfractionated heparin (UFH) was administered in 32.8% of patients, low-molecular-weight heparin (LMWH) in 13.8%, and GP IIb/IIIa inhibitors in 26.8%. Medication overdosing was associated with a significant increase in major bleeding, 13.6% with excess UFH, 12.5% with excess LMWH, and 17.5% with excess GP IIb/IIIa inhibitors. It also showed that paradoxically, those patients for whom fear of bleeding prevented the physician from administering antithrombotic drugs (such as older adults) were the most likely to receive an excess dose.

A recent CRUSADE study also evaluated the predictors and consequences of blood transfusions among patients with NSTE ACS.[66,70] The rate of transfusion among patients with NSTE ACS who did not undergo coronary artery bypass graft surgery was 10.3%, and renal insufficiency, advanced age, and female gender were among the strongest predictors of blood transfusion use. The adjusted risk of mortality associated with transfusion was approximately two thirds higher (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.48 to 1.88). Thus, CRUSADE analyses have reinforced the concept that the correct dosing of recommended antithrombotic agents is equally important as the use of these drugs.

Guideline Adherence and Improved Survival

Data from the CRUSADE registry have shown that the in-hospital mortality rate in real-world NSTE ACS patients is 4.9%, which is much higher than that observed in randomized controlled trials (1.5% to 1.9%).[5] It was also shown that evidence-based guidelines for ACS treatment were underused, and increases in guideline adherence resulted in a significant reduction in mortality rates. Hospitals with the highest adherence scores had the lowest incidence of in-hospital mortality (4.2%). Hospitals with the lowest adherence scores had a higher mortality rate (6.3%). Thus, for

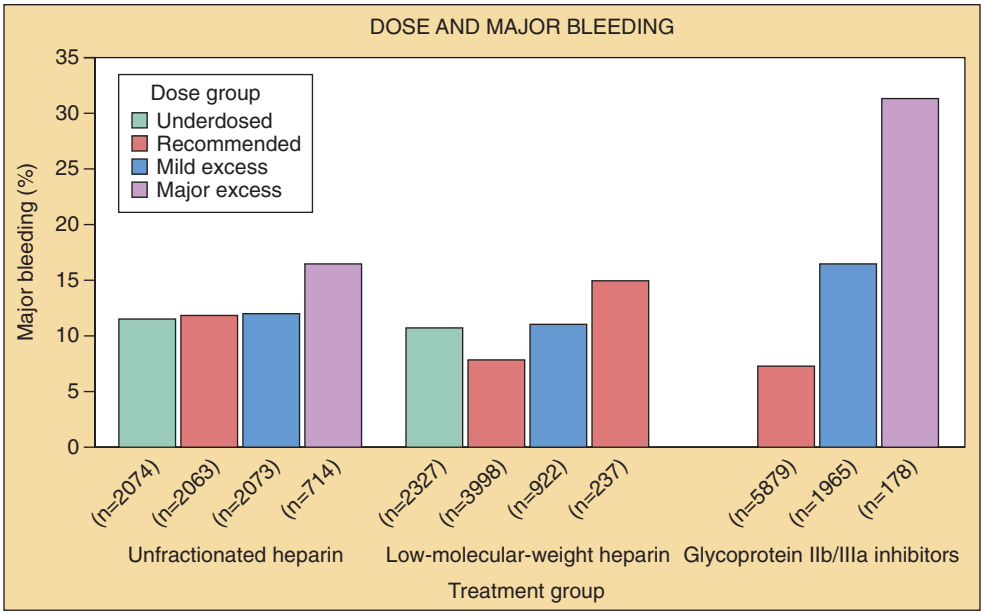


FIGURE 5–6 Antithrombotic dosing and major bleeding (CRUSADE).

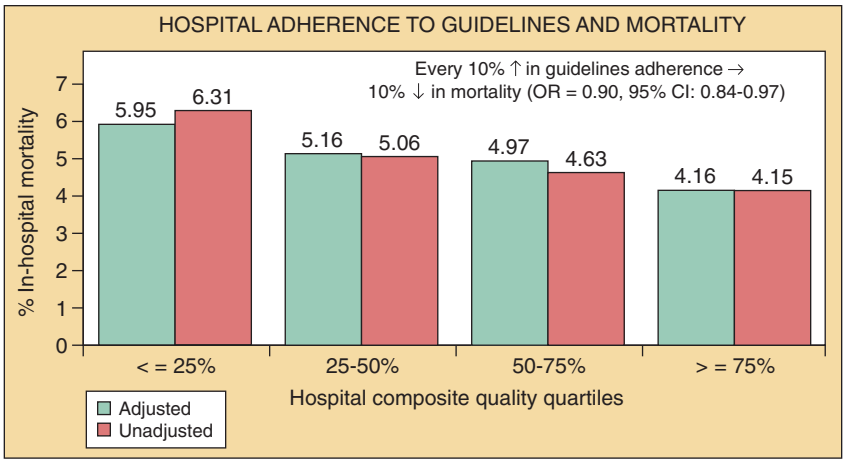


FIGURE 5–7 Hospital performance and outcomes in CRUSADE.

every 10% increase in guideline adherence, there was a 10% reduction in mortality (OR, 0.90; 95% CI, 0.84 to 0.97; Fig. 5-7). Similarly, an analysis from the NRMI-4 database of patients hospitalized between 2000 and 2002 showed an unadjusted in-hospital mortality rate of 14.3% in patients with STEMI and 12.5% for NSTEMI, which were much higher than expected.[6] This was related to underuse of proven therapies. Between 12% and 15% of patients did not receive aspirin within 24 hours, approximately 20% did not receive a beta blocker, and many patients did not undergo basic procedures such as catheterization, typically in the NSTE population.

Hospital Performance and Acute Coronary Syndrome Outcomes

Hospitals are under increasing pressure to improve their quality of care. Governmental agencies, accreditation organizations, and insurance payers have mandated objective measures of adherence to performance measures.[30-32] Previously, there were little data to show the association between hospital process performance and outcomes. CRUSADE researchers reported the results of comparison of hospital performance in the United States, which showed that patient outcomes demonstrating improved mortality were associated with higher levels of guideline adherence by a hospital.[5] Overall, the nine ACC-AHA guideline-recommended treatments were adhered to in only 74% of eligible cases. There was a wide variation in guideline adherence score of each individual hospital, from as low as 40% to as high as 85% (Fig. 5-8). The composite guideline adherence rate significantly correlated with in-hospital mortality, with observed mortality rates decreasing from 6.3% for the lowest adherence quartile to 4.1% for the highest adherence quartile. CRUSADE also showed that nonteaching or for-profit hospitals tend to score lower than academic or nonprofit hospitals.[51] Interestingly, the outcome of AMI patients was also shown to be better when the care was provided by a cardiologist. This is probably related to better implementation of recommended medical therapy and the higher use of reperfusion therapy by cardiologists, which could account for most of the observed difference in outcome.

With the CRUSADE quality improvement initiative, there was improvement over time in overall adherence as well as the increased use of short-term and long-term therapies for ACS. This generated significant interest and enthusiasm for the CRUSADE quality improvement initiative at all levels, from physicians at individual hospitals to national health care payers.[19]

ACTION Registry–GTWG

The American College of Cardiology Foundation's NCDR and the American Heart Association's GWTG have recently joined forces to fight heart attacks by creating a unified national ACS registry to measure and improve cardiovascular patient care.[71] This collaboration joins two leading national coronary artery disease registries, the NCDR ACTION Registry and the AHA GWTG–CAD Registry, to create the largest and most comprehensive national cardiovascular patient database ever

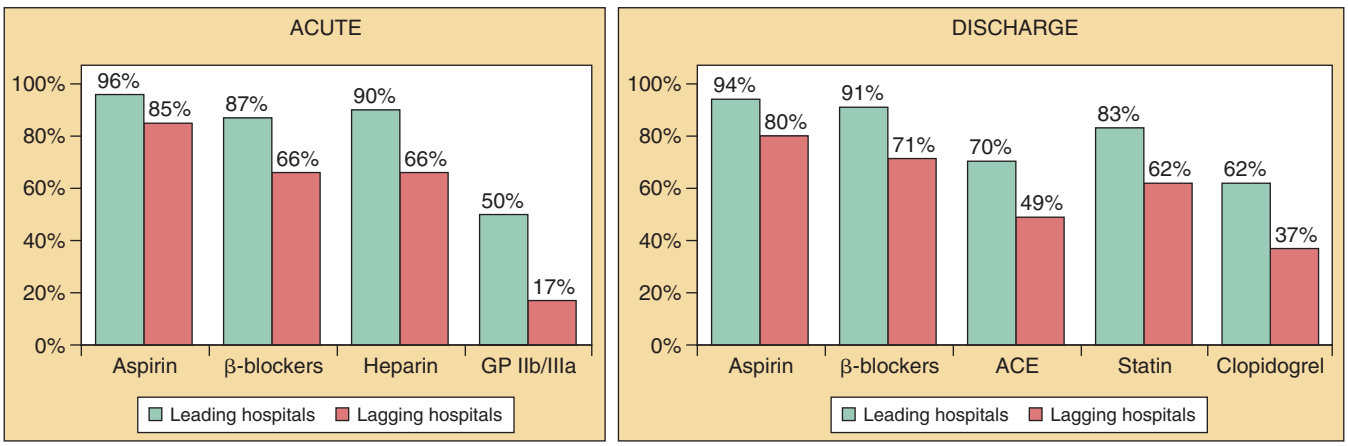


FIGURE 5–8 Variability in health care at leading and lagging centers.

developed by the medical profession. This new registry, called ACTION Registry–GWTG, will establish the national standard for understanding and improving the quality, safety, and outcomes of care provided for patients with coronary artery disease. It will bring the best of both programs to a single registry, ultimately offering more benchmarking and quality improvement power to hundreds and eventually thousands of hospitals across the country that provide care for ACS patients.

SUMMARY

Significant advances in ACS treatment have been made over the last 2 decades, correlating with improvements in patient outcomes. However, gaps still remain to be filled to allow more widespread implementation of proven therapies, particularly in the highest risk groups. Adherence to ACC-AHA guideline-recommended treatment is strongly associated with decreased mortality in ACS patients. Real-world registries are playing a key role in effective translation and implementation of evidence-based treatment guidelines, and providing measures of quality improvement.

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SECTION II

Disease-Based Perspectives

CHAPTER 6

Pathogenesis of Stable and Acute Coronary Syndromes

Jacob Fog Bentzon and Erling Falk

Vascular lesions that resemble atherosclerosis have been described in Egyptian and Renaissance mummies,[1,2] but death and disabling symptoms caused by atherosclerosis were probably rare before the late 18th century and remained relatively uncommon until the beginning of the 20th century.[3] From this time on, the incidence of symptomatic atherosclerosis increased dramatically in Europe and the United States until the mid-1900s,[4] and increases of comparable magnitude occurred later or are now occurring in many other parts of the world, making atherosclerosis a leading global cause of death and disability today.[5]

Pathoanatomic descriptions of the disease span the last 250 years. In 1786, Edward Jenner proposed coronary atherosclerosis to be the cause of angina pectoris—the disease described few years before by Heberden—and, by the mid-1800s, the histology of atherosclerosis was already described in detail by Virchow and others.[6] Angina pectoris was recognized to be a deadly disease, but the most common link between atherosclerosis and death (i.e., myocardial infarction [MI] caused by coronary thrombosis) was not described until the accounts of Weigert and Osler in 1880 and 1910,[7] respectively. It would take an additional 50 years before Constantinides, Chapman, and Friedman discovered the mechanism underlying most cases of coronary thrombosis.[8-10] They found that most coronary thrombi are precipitated by atherosclerotic plaque rupture, whereby highly thrombogenic plaque components are exposed to the flowing blood. It was also noted that some thrombi formed on nonruptured plaques with minimal surface irregularities, and later the term *plaque erosion* was introduced to describe this phenomenon.[11] Today, we know that not only MI, but also unstable angina and most cases of sudden coronary death, are caused by thrombosis superimposed on ruptured or eroded plaques. This shared pathogenesis is reflected in the collective clinical term *acute coronary syndrome* (ACS).

In this chapter, we will review the pathogenesis of atherosclerosis, its early onset in life and variable progression rate, the heterogeneity of atherosclerotic plaques, and how the heterogenous nature of the disease translates into different clinical presentations.

CLASSIFICATION AND PROGRESSION OF ATHEROSCLEROSIS

Atherosclerosis is a chronic, inflammatory, fibroproliferative disease of the intima of large and medium-sized arteries characterized by early retention and modification of atherogenic lipoproteins, recruitment of monocytes and T lymphocytes, and subsequent accumulation of abundant fibrous tissue.[12] The causal agent is an elevated level of apolipoprotein B (apo B)–containing lipoproteins in the blood, but other risk factors such as male gender, hypertension, diabetes, and genetic susceptibility modify the disease by only partly understood mechanisms.

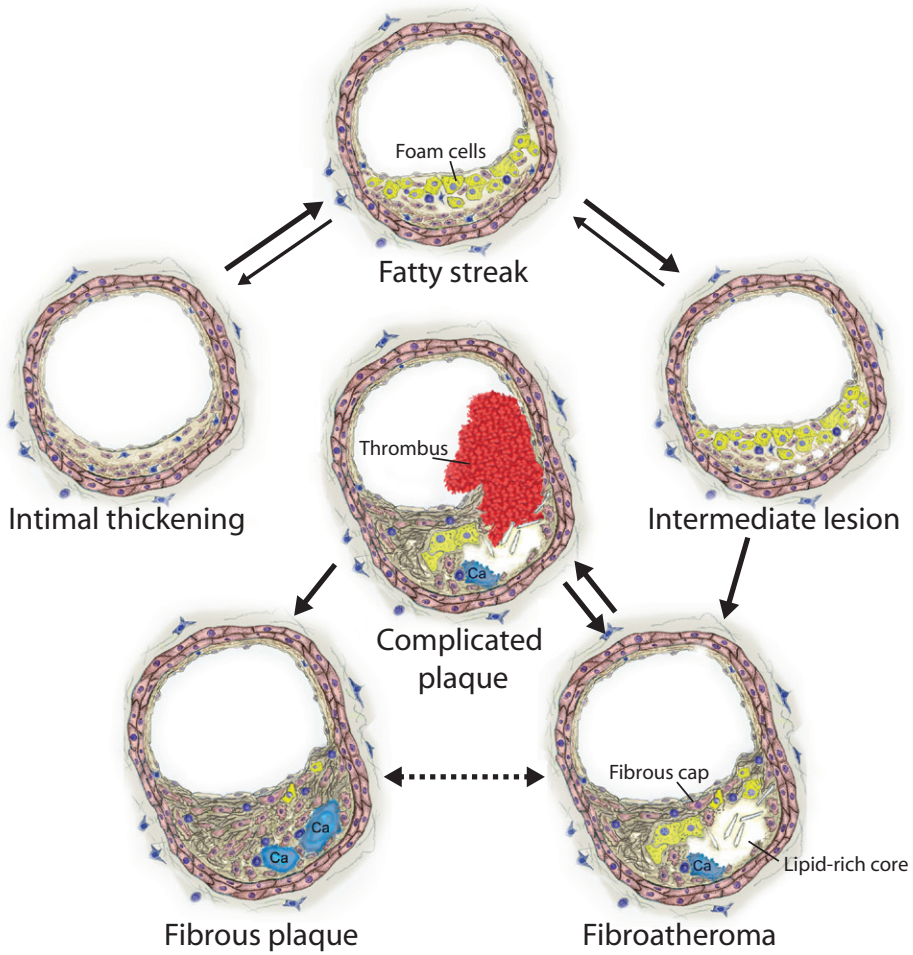

FIGURE 6–1 Simplified version of the pathogenesis of atherosclerosis as described by the Committee on Vascular Lesions of the Council on Atherosclerosis, AHA. The nomenclature is not completely identical to that endorsed by the AHA.[15] Because some advanced lesion types (e.g., fibroatheromas, fibrous plaques) evolve simultaneously in life, their interrelationships are difficult to resolve in autopsy studies. Ca, calcification.

Classification

Atherosclerosis begins to develop early in life, but the speed of progression is unpredictable and varies markedly among different subjects. However, even in those most susceptible to the disease, it usually takes several decades to develop obstructive or thrombosis-prone plaques. In a series of key papers, the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA), reviewed how the pathogenesis of atherosclerosis can be inferred from histologic analyses of lesions at defined arterial locations in persons from childhood to old age.[13-15] The AHA council also proposed a widely used classification scheme for atherosclerotic lesion types, which was updated in 2000.[16] An alternative classification, which emphasizes the link between atherosclerotic plaque morphology and clinical presentations, was suggested by Virmani and colleagues.[17]

Figure 6-1 displays a simplified version of the AHA classification and the proposed sequence of lesion progression. Atherosclerosis is a heterogeneous disease and a single patient with advanced disease will typically harbor all these different lesion types at different sites of the coronary tree (Fig. 6-2). However, also within very short artery segments, several lesion types may be identified in close proximity by serial sectioning. The latter type of variation stems from the

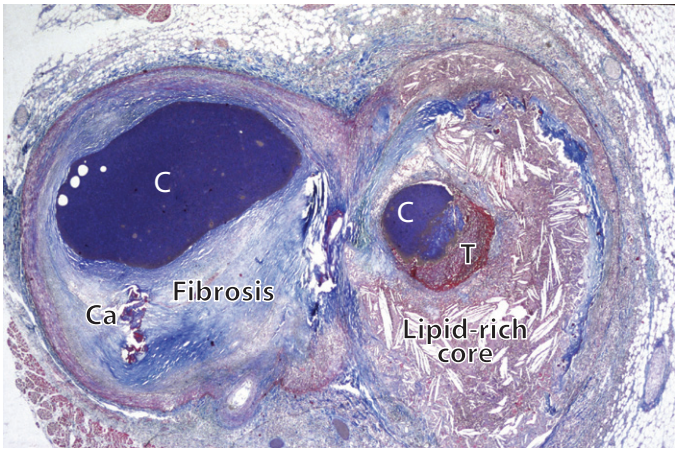

FIGURE 6–2 Severe atherosclerosis, a variable mixture of lesion types. This cross-sectioned coronary artery bifurcation illustrates a fibrous plaque *(left)* in the left circumflex and a complicated plaque with a nonocclusive thrombosis in the obtuse branch *(right)* (elastin-trichrome stain). C, contrast in the lumen; Ca, calcification; T, thrombosis.

fact that current classifications of atherosclerosis assign lesion types based on thin cross sections (a few microns) of a three-dimensional structure that vary considerable in morphology in the longitudinal direction.[18]

Normal Arterial Intima

The arterial wall is composed of three layers—the tunica intima (inner layer), the tunica media (middle layer), and the tunica adventitia (outer layer). The intima is defined as the region that extends from the arterial lumen, including the endothelium, to the internal elastic lamina. It is often no more than a few cell layers thick, but in discrete, reproducible regions of the normal arterial tree, the intima is thickened and consists of a subendothelial proteoglycan-rich layer and a deeper musculoelastic layer with smooth muscle cells (SMCs) and elastic fibers.[13] These intimal thickenings presumably form as a physiologic adaptation to low and/or oscillatory wall shear stress. They are mainly located near vessel branch points or along inner vessel curvatures.[19,20] In humans and animals without atherosclerosis, these sites are further characterized by changes in the shape and replication rate of endothelial cells, expression of adhesion molecules, and recruitment of dendritic cells from circulating monocytes.[21,22]

Intimal thickenings are affected early during atherogenesis; they are *atherosclerosis-prone*, and the rate of progression is higher here than at other arterial sites. With age, adjacent intima is increasingly involved, so that most of the epicardial coronary arteries are affected in persons dying from an ACS in older age.[23]

Progression of Atherosclerosis

Foam Cell Lesions

The key initiating mechanism in atherosclerosis appears to be the retention of apo B-containing lipoproteins, primarily low-density lipoprotein (LDL), to extracellular proteoglycans in the arterial intima.[24,25] Extracellular lipid droplets of aggregated and fused LDL particles in the proteoglycan-rich layer of intimal thickenings represent the first microscopic sign of atherosclerosis in children and young adults.[26,27]

Subendothelial modification of the retained lipoproteins (e.g., aggregation, fusion, oxidation) by enzymes and oxidative radicals yields a range of bioactive lipids.[28] The modified lipoprotein moieties, in turn, act as proinflammatory mediators that stimulate the recruitment, differentiation, and replication of monocyte-derived macrophages through induction of endothelial adhesion molecules, chemoattractants, and growth factors.[12,29] In the intima, macrophages avidly engulf modified, but not native, LDL particles through scavenger receptors,[30] and their cytoplasm becomes packed with droplets of cholesteryl esters, giving them the appearance of foam cells. T lymphocytes and dendritic cells are also present from this stage onward, and immune responses are an important modulator of the atherosclerotic process.[31]

Foam cells accumulate in the luminal, proteoglycan-rich layer of the intima and, when several layers of foam cells have formed, they may be visible to the naked eye on the intimal surface of arteries as yellow *fatty streaks*. Foam cell lesions are harmless and are fully reversible if the local pathologic stimuli that caused their formation dissipate. For instance, they are present in the coronary arteries in 50% of infants during the first 6 months of life, but their number declines in subsequent years.[32] At puberty, they usually reappear in atherosclerosis-prone regions of the arterial tree,[32] but only some of these progress to more advanced stages of atherosclerosis.

Intermediate Lesions

In some foam cell lesions, retention of lipoproteins from the circulation continues and is enhanced, and isolated extracellular lipid pools begin to accumulate in the musculoelastic layer beneath the layers of foam cells.[14] There is dispersion or local loss of the intimal SMCs where the pools form, but there is no gross disruption of the normal structure of the intima.[14,33] Recent studies have suggested that the formation of lipid pools is accentuated by failure of the normal phagocytic clearance of apoptotic foam cells.

Foam cell lesions with basal pools of extracellular lipid are termed *intermediate lesions*, sometimes referred to as pathologic intimal thickening,[17] because they represent the historically controversial link between the innocuous and widespread fatty streaks, and the clinically relevant, more localized advanced lesions.[14] Intermediate lesions are evident by 20 to 30 years of age in atherosclerosis-prone regions of the coronary arteries.[14,34]

Fibroatheromas

The critical step that turns the reversible precursor lesions (foam cells and intermediate lesions) into irreversible advanced (fibro)atheromas is the conversion of the isolated lipid pools into one or more confluent lipid-rich cores (or, synonymously, necrotic core, lipid core, or atheromatous core). This process irreversibly disrupts the normal structure of the intima with degradation of the extracellular matrix and death of local SMCs and leaves behind a matrix-devoid, acellular gruel of lipids (cholesteryl esters, free cholesterol, phospholipids, triglycerides) and cell debris.

Foam cell apoptosis combined with defective phagocytic clearance of apoptotic cells contribute to the formation and growth of the lipid-rich core.[35] Cell death, both apoptotic and other forms, occurs at the margin of the core,[36] and macrophage-specific antigens and apoptotic microparticles are present within the atheromatous material.[37,38] Lipoproteins may also insudate directly from the blood into the core without passing foam cells, and this may actually be the quantitatively dominant source of the lipids.[39] In more advanced plaques, intraplaque hemorrhage into the core from neovessels may be an important source of lipids, especially of free cholesterol.[40] Neovascularization extending from the adventitial vasa vasorum into the base and shoulder regions of the plaque is a common feature at the fibroatheroma stage.

The piece of tissue that separates the lipid-rich core from the blood is called the *fibrous cap*. This structure plays an immensely important role for the clinical consequences of atherosclerosis as detailed below. The fibrous cap initially consists of the proteoglycan-rich layer of the normal intima (with isolated intimal SMCs and infiltrating foam cells), now separated from the underlying media by the developing lipid-rich core. Gradually, however, the original intimal tissue is replaced and expanded by collagen-rich fibrotic tissue, which eventually grows to become the quantitatively dominant component in most advanced plaques.[41] The AHA classification reserves the term *fibroatheroma* for lesions with fibrosis and uses the term *atheroma* for lesions with only normal intimal connective tissues[15]; others use the term *fibroatheroma* collectively for both lesion types.[17]

The fibrous matrix of atherosclerotic plaques is produced by synthetic-type SMCs which, compared with the normal contractile SMCs of the arterial media, are ultrastructurally dominated by organelles involved in protein synthesis (rough endoplasmic reticulum and Golgi apparatus) and show increased capacities for proliferation, migration, and matrix synthesis.[42] A few synthetic-type SMCs are present in the normal intima, but they increase substantially in number at the fibroatheroma stage.[15] A novel hypothesis has implicated circulating, bone marrow–derived progenitor cells in the

recruitment of these cells to the atherosclerotic plaque,[43,44] but recent experimental studies in mouse models have shown that only proliferation and migration of local cells, presumably local contractile SMCs, are contributing factors.[45-47] Indeed, contractile SMCs in the intima and media are able to modulate to the matrix-producing synthetic phenotype, and this phenotypic modulation appears to be key in the formation of the fibrous component of atherosclerosis.[42] In recent years, the molecular switches that control SMC phenotype have begun to be unravelled,[48] but the extracellular cues that direct the process are incompletely understood.

A third characteristic component of fibroatheromas is calcifications. Microscopic calcium granules are found intracellularly in some SMC organelles and extracellularly throughout the lipid-rich core.[49] These initial microscopic foci of calcification may expand to form larger lumps and plates of calcium deposits, especially at the base of lipid-rich core. This may be a regulated process reminiscent of bone formation facilitated by phenotypically modulated, osteogenic SMCs, or by other cell types in the plaque.[50,51] Calcifications can constitute most of the plaque volume.

Fibrous Plaques

The fibroatheroma is the hallmark of atherosclerosis and what named the disease. *Athére* is Greek for gruel or porridge and refers to the lipid-rich core, and *scleros* means hard, which describes the fibrotic and often calcified encapsulating tissue. However, many advanced plaques at autopsy are not fibroatheromas but are fibrous plaques consisting of relatively homogeneous fibrotic tissue with calcifications, but no lipid-rich core. Their genesis is not fully understood. Some pathologists believe that the development of a lipid-rich core is the prerequisite of fibrosis,[16] and serial sectioning often reveals that a lipid-rich core is present in the upstream or downstream vicinity of the section with fibrous plaque. If this is not the case, an originally formed lipid-rich core may have disappeared because of local quiescence of the atherosclerotic process or through plaque rupture with core extrusion and subsequent healing (see later). Regression studies in monkeys have indicated that lipid-lowering can turn fibroatheromas into fibrous plaques.[49] On the other hand, recent studies have shown that some fibrous plaques may have a separate genesis, developing in the absence of a preceding lipid-rich core and fatty streak.[34]

Complicated Plaques

When thrombus is present, with or without luminal obstruction, the lesion is called a complicated plaque and is further subdivided by the presence or absence of plaque rupture. With rupture (also known as plaque fissuring), the thrombus is in direct connection with the highly thrombogenic lipid-rich core of a fibroatheroma through a disruption of the fibrous cap (Fig. 6-3). When no such rupture can be identified despite a thorough search, the term *plaque erosion* is used. Both intermediate lesions, fibroatheromas, and fibrous plaques may be complicated by plaque erosion. Plaque disruption is sometimes used synonymously with plaque rupture and sometimes as a collective term for rupture and erosion. Some pathologists acknowledge a third, but rare, category of complicated plaques, calcified nodule.[17]

PLAQUES CAUSING STABLE ANGINA

Over the years, plaques can grow to become so voluminous that the arterial lumen is reduced below a critical point and ischemia sets in, leading to stable angina pectoris.[41] Most advanced plaques in humans, however, will never cause symptoms. This is partly because stenosis is not flow-limiting until geometrically severe and partly because the artery often dilates during atherogenesis.[52]

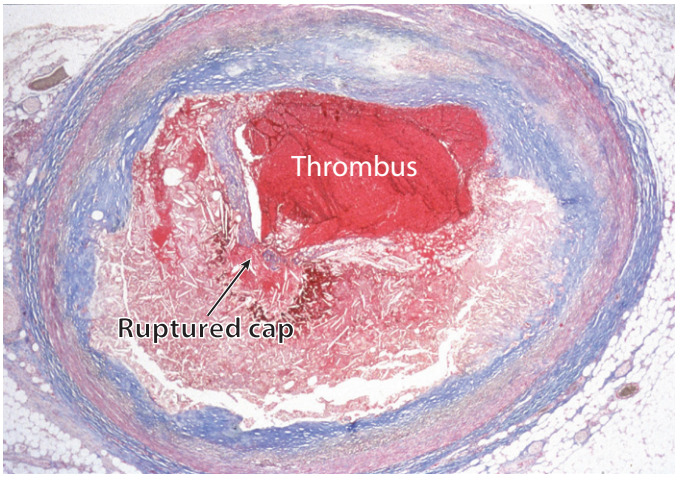

FIGURE 6–3 Plaque rupture. Shown is a cross section of a ruptured plaque with superimposed occlusive thrombosis. There is a structural defect in an extremely thin fibrous cap, with exposure of the highly thrombogenic core material to the blood (elastin-trichrome stain).

Determinants of Stenosis Severity

The severity of flow obstruction in atherosclerotic arteries depends on plaque size, vasoconstriction (spasm), and remodeling of the vessel wall. During atherosclerotic lesion formation, the local vessel segment may expand and thereby preserve the lumen (expansive remodeling, also known as positive or outward remodeling),[53] or shrink to diminish it (constrictive remodeling, also known as negative or inward remodeling; Fig. 6-4).[54] Expansive remodeling is more common than constrictive remodeling.[55,56]

Autopsy studies and intravascular ultrasound (IVUS) examination of coronary arteries have shown that the extent and direction of arterial remodeling are at least as important as plaque size in determining stenosis severity.[54,55,57,58] Therefore, imaging of the lumen of an artery by coronary angiography or other techniques is not useful for diagnosing the presence of atherosclerotic plaque or measuring changes in atherosclerotic plaque size with medical intervention.[59]

The mechanisms of arterial remodeling in atherosclerosis have not been fully clarified. Expansive remodeling may partly be a homeostatic response of the nondiseased vessel wall at sites of eccentric plaque formation to maintain normal shear stress. However, increasing evidence has suggested that it is predominantly a pathophysiologic process, in which proteolytic enzymes secreted by plaque macrophages cause the underlying media to thin and yield. This is supported by the fact that plaque growth is frequently followed by a paradoxical increase in luminal area in mice and humans,[59,60] local expansion occurs beneath atherosclerotic plaques in mice,[60] and the direction and extent of remodeling are associated with the composition of the local plaque.[61,62] Initial autopsy studies have indicated that expansive remodeling is only possible until the atherosclerotic plaque constitutes approximately 40% of the area within the internal elastic lamina,[53] but this may have been an artifact of the variable used to measure plaque size. A recent IVUS study has shown that the capacity of the vessel wall to remodel is unrelated to plaque burden.[63] The mechanism of constrictive remodeling have not been studied in detail, although it may be related to plaque rupture followed by healing (see later).

Superimposed on arterial remodeling, local vasoconstriction may have a profound effect on flow obstruction, and

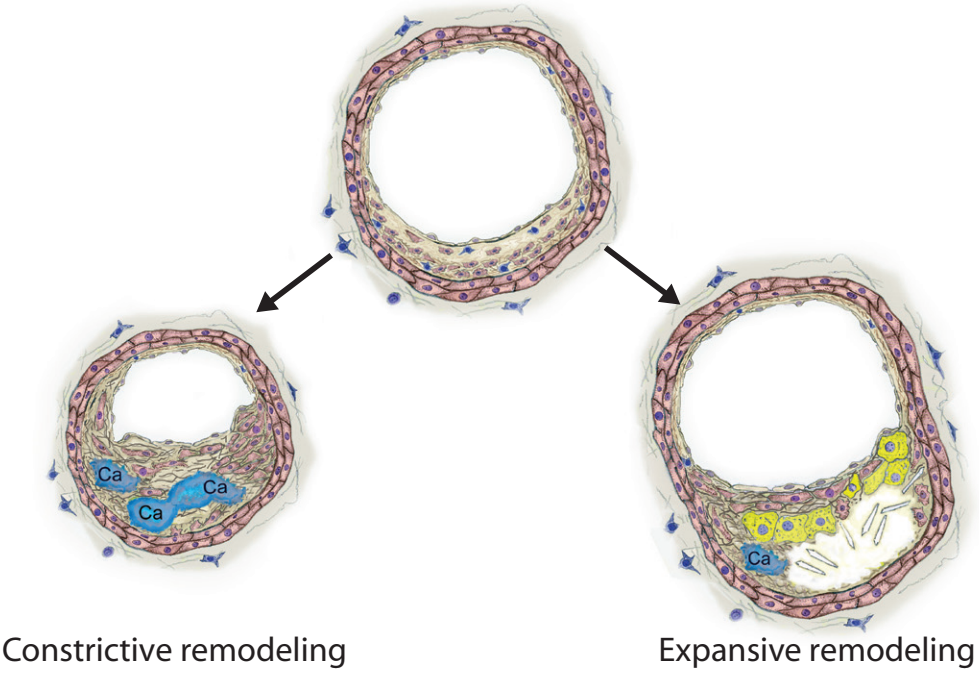

FIGURE 6–4 Impact of arterial remodeling on stenosis formation. *Left,* Plaque growth with constrictive remodeling compromising the lumen. *Middle,* Prelesional arterial dimensions. *Right,* Plaque growth with expansive remodeling, leading to preservation or even an increase in luminal area. Ca, calcification.

paradoxical exercise-induced vasospasm is frequent in stable angina pectoris.[64] These dynamic changes should be distinguished from structural remodeling of the artery.

Development of Stenoses

Resting blood flow through a stenosed artery is not significantly affected until the luminal area is reduced by approximately 80% (or the diameter by 50%), although the flow reserve is decreased with less reduction. Stenoses of this magnitude are caused by a fibroatheroma or fibrous plaque. The plaque may be substantially calcified and the local vessel segment is often negatively remodeled,[65] but the relationship among plaque morphology, arterial remodeling, and stenosis formation is not consistent.

A small proportion of culprit plaques in stable angina have residual thrombus[66] and at postmortem examination there may be evidence of previous occlusive thrombosis in the form of a multichannel lumen, suggesting recanalization, or myocardial scarring in the region supplied by the artery.[67] Furthermore, a special nonuniform pattern of dense type I (older) and loosely arranged type III (younger) collagen, considered to indicate healed plaque rupture, has been identified in many coronary plaques, particularly in those that cause chronic high-grade stenoses.[68] Often, several healed rupture sites are present in plaques and the number of healed ruptures correlates with the severity of stenosis.[69]

The combined findings indicate that subclinical plaque ruptures with thrombus formation may be important in chronic stenosis formation. Indeed, the vast majority of plaque ruptures are not lethal and most are clinically silent.[70] In these cases, SMCs heal the rupture site and organize residual thrombus by secreting an extracellular matrix rich in glycosaminoglycans and type III collagen.[68] This restores the integrity of the plaque surface but may cause rapid plaque growth,[68,69] and scar-like contraction of the healing SMCs pulling on fibrin fibrils may lead to concomitant constrictive remodeling.[62,71]

The central role of plaque healing in stenosis formation is consistent with clinical observations. Serial angiography has shown that many coronary artery stenoses develop in a phasic rather than linear manner, with chronic high-grade stenoses forming at sites that were only insignificantly narrowed the year before.[72]

PLAQUES CAUSING ACUTE CORONARY SYNDROMES

Unstable angina and acute MI are almost always caused by a luminal thrombus superimposed on an atherosclerotic plaque with or without concomitant vasospasm.[73] In ST-segment elevation myocardial infarction (STEMI), the thrombus is usually occlusive and sustained, whereas in unstable angina and non-STEMI (NSTEMI), the thrombus is more often nonocclusive and dynamic. Acute or organized thrombus is found in most victims of sudden coronary death; the rest die with severe coronary disease and myocardial scarring (old MI) in the absence of thrombosis.[17,73] Rare causes of ACS include emboli, artery dissection, vasculitis, cocaine abuse, and trauma.

The most frequent cause of coronary thrombi is plaque rupture. In plaque rupture, a structural defect in the fibrous cap exposes the highly thrombogenic core to the blood (see Fig. 6-3).[74] By definition, when no plaque rupture is identified, despite a thorough search, the term *plaque erosion* is used. Table 6-1 presents an overview of autopsy studies in which fatal coronary thrombi were identified and the underlying plaques studied carefully to detect plaque rupture. This worldwide survey shows that plaque rupture is the major cause of coronary thrombosis, responsible for approximately 75% of cases. Plaque rupture is a less frequent cause of thrombosis in women (60%) than in men (78%), and is rare in a very small subgroup of patients—namely, premenopausal women, who constitute less than 1% of heart attack victims.[75]

TABLE 6–1 Overview of Autopsy Studies of Coronary Thrombi*

Study (Year)	Cause of Death	Gender	Thrombi, No. of Cases	Rupture, No. of Cases (% of Total)
Chapman (1965)[10]	—	—	19	19 (100)
Constantinides (1966)[8]	—	—	17	17 (100)
Friedman et al (1966)[9]	AMI + SCD	—	40	39 (98)
Bouch & Montgomery (1970)[106]	AMI	Female	32	26 (81)
		Male	56	45 (80)
Sinapius (1972)[107]	AMI	—	91	68 (75)
Horie et al (1978)[108]	AMI	—	76	69 (91)
Falk et al (1983)[79]	AMI	Female	12	8 (67)
		Male	37	32 (86)
Tracy et al (1985)[109]	SCD	—	32	26 (81)
El Fawal et al (1987)[110]	SCD	—	61	39 (64)
Yutani et al (1987)[111]	AMI	Male	83	52 (63)
Richardson et al (1989)[112]	—	—	85	71 (84)
van der Wal et al (1994)[11]	AMI	—	20	12 (60)
Shi et al (1999)[113]	AMI	—	61	56 (92)
Arbustini et al (1999)[101]	AMI	Female	107	67 (63)
		Male	184	150 (82)
Kojima et al (2000)[114]	AMI	Female	26	18 (69)
		Male	74	63 (85)
Farb et al (1996)[115]	SCD	Female	16	5 (31)
		Male	34	23 (68)
Davies (1997)[116]	SCD	Female	27	16 (59)
		Male	134	113 (84)
		—	41	14 (34)
Burke et al (1999)[117]	SCD	Male	70	44 (63)
Burke et al (1998)[75]	SCD	Female, <50 yr	16	1 (6)
		Female, ≥50 yr	10	7 (70)
All	AMI + SCD	Both	1461	1100 (75)
		Males	672	522 (78)
		Females	246	148 (60)

* Plaque rupture is the predominant cause of fatal acute coronary syndromes. Worldwide, 1100 (75%) of 1461 fatal coronary thrombi were precipitated by plaque rupture.
AMI = acute myocardial infarction; SCD = sudden coronary death; —, not reported.

A few studies have reported that diabetes, smoking, and the level of hyperlipidemia are associated with the mechanism of thrombosis in ACS but, except for gender and menopause, no consistent relationships have been demonstrated.[76]

Thrombus Formation

The magnitude of the thrombotic response to ruptured or eroded plaques is extremely variable. Most frequently, only a small mural thrombus seals the thrombogenic plaque material, and only occasionally does a major life-threatening luminal thrombus evolve. Probably the determinants are those of the classic triad of Virchow: (1) thrombogenicity of the exposed plaque material; (2) local flow disturbances; and (3) systemic thrombotic propensity. With plaque rupture, cap collagen and the highly thrombogenic lipid-rich core, enriched in tissue factor–expressing apoptotic microparticles, are exposed to the thrombogenic factors of the blood.[38,77] The mechanism of thrombus formation on eroded plaques is more controversial. Whatever the cause of endothelial denudation, it is a relatively weak thrombogenic stimulus; thus, flow disturbances and systemic thrombogenic factors, such as platelet hyperaggregability, hypercoagulability, circulating tissue factor, and/or depressed fibrinolysis (vulnerable blood), may be particularly important in this setting.[78]

The interval between plaque rupture and syndrome onset is not easily assessed because rupture in itself is asymptomatic and the following thrombotic process is highly unpredictable. Plaque material is sometimes found interspersed in the thrombus,[11,79] indicating that severe thrombosis followed immediately after plaque rupture. In other cases, the thrombotic response is dynamic: thrombosis and thrombolysis, often associated with vasospasm, tend to occur simultaneously, causing intermittent flow and the formation of a layered thrombus developing over days (Figs. 6-5 and 6-6).[76] While blood flow continues over the culprit lesion, microemboli of plaque material and thrombus may be washed away, leading to distal embolization.[80] Iatrogenic embolization may occur with percutaneous coronary intervention. The distal emboli from either source may cause microvascular obstruction that prevents myocardial perfusion, despite a recanalized infarct-related coronary artery.[80]

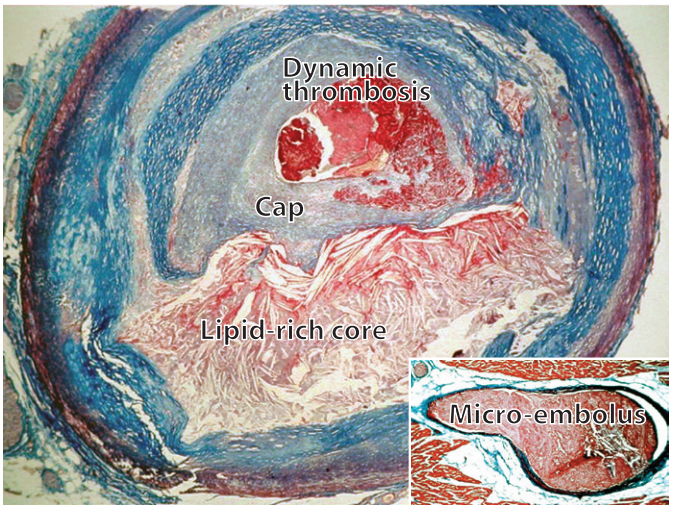

FIGURE 6–5 Dynamic thrombosis. In acute coronary syndromes, the thrombotic process is often dynamic with alternating thrombosis and thrombolysis, indicated by a layered structure of the thrombus. It is often accompanied by local vasoconstriction and distal thromboembolism, which may prevent optimal myocardial perfusion, despite a patent culprit artery. *Inset,* Microemboli downstream in the myocardium.

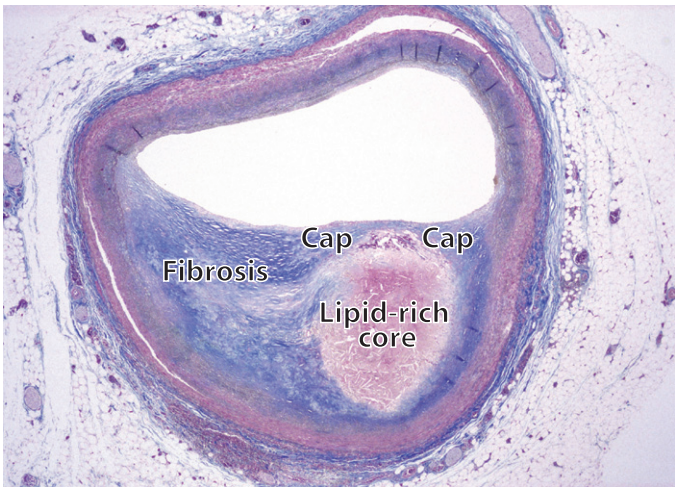

FIGURE 6–7 Rupture-prone plaque. The large lipid-rich core is covered by a thin fibrous cap. A point of clarification—it has become a paradigm that *plaque inflammation* characterizes the rupture-prone plaque, but note that the bulk of the plaque consists of acellular necrosis and hypocellular fibrosis, with no or minimal inflammation. What characterizes ruptured plaques is *cap inflammation*, with degradation of connective tissue fibers and local loss of SMCs within the fibrous cap.

Plaque Vulnerability

To predict which plaques are at risk of precipitating thrombosis and how this could be prevented, much attention has been directed toward identifying so-called vulnerable plaques (or, synonymously, thrombosis-prone or high-risk plaques). These plaques are at high short-term risk of thrombosis.[74] The rationale is clear—if vulnerable plaques could be rendered harmless before they would otherwise cause thrombosis, atherosclerosis would be a much less dangerous disease.

Because the mechanisms of superimposed thrombosis can be divided into two groups, plaque rupture and erosion, so can vulnerable plaques. These are referred to as rupture-prone and erosion-prone plaques.

Rupture-Prone Plaques

Plaque rupture tends to occur at the cap margin, or shoulder region, where the cap is often thinnest and therefore weakest.[81] In a minority of cases, a temporary increase in the mechanical force (trigger) imposed on the cap appears to have precipitated the rupture. Recognized triggers include extreme physical activity, severe emotional stress, sexual activity, cocaine or amphetamine abuse, cold exposure, acute infections, or simple daily activities.[82,83] Sometimes, whole populations are exposed to the same potential trigger simultaneously—for example, the Northridge earthquake in Los Angeles County, January 17, 1994. During the day of the earthquake, the incidence of acute coronary syndromes was almost twice the normal level, but in the following weeks it was lower than usual.[84] This indicates that a trigger may determine the exact timing of a coronary event in vulnerable individuals, but that the event in most cases would have occurred anyway within a few weeks. Also, the fact that exercise stress testing in individuals with advanced coronary atherosclerosis rarely triggers an ACS suggests that plaque morphology ultimately plays a more important role than triggers in determining whether plaque rupture will occur.

Box 6-1 lists the features that characterize ruptured plaques. By inference, the same features, except thrombus, are assumed to characterize rupture-prone plaques. The risk of plaque rupture seems to depend primarily on fibrous cap thickness and lipid-rich core size, less on plaque size, and not on severity of stenosis (Fig. 6-7).

Thin Fibrous Cap. Only very thin fibrous caps are at risk of rupturing. In the coronary arteries, the mean fibrous cap thickness in ruptured plaques at autopsy is 23 μm (the

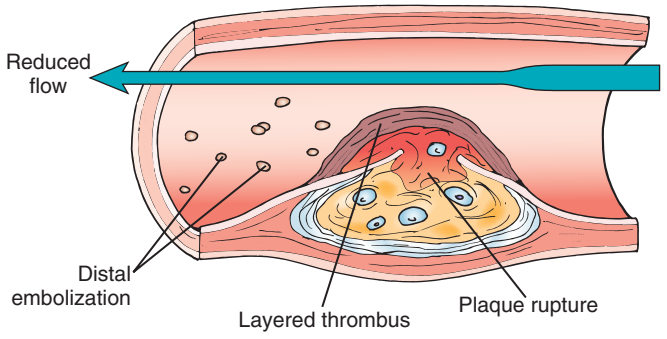

FIGURE 6–6 Culprit lesion of unstable angina. Shown is plaque rupture with superimposed dynamic thrombosis. The layering of thrombus reveals the stepwise progression. Microscopic distal emboli are seeded to the myocardium supplied by the artery.

BOX 6-1 Features of Ruptured Coronary Plaques*

- Thrombus
- Weak fibrous cap
  - Thin (<65 μm)
  - Macrophage infiltration (inflammation)
  - Few SMCs (apoptosis)
- Large lipid-rich core
  - Hemorrhage into the core
- Other features
  - Expansive remodeling
  - Neovascularization
  - Adventitial inflammation

*By inference, the same features, except for thrombus, are assumed to characterize rupture-prone plaques.

diameter of just one foam cell) and 95% of ruptured fibrous caps are less than 65 μm thick.[85] Based on these observations, Virmani and colleagues have suggested the term *thin-cap fibroatheromas* (TCFAs) for coronary fibroatheromas with a fibrous cap thickness less than 65 μm.[17] This group of plaques is expected to encompass the rupture-prone plaques and, importantly, they can be detected in vivo by novel high-resolution intravascular imaging devices.[86]

The critical thickness of the fibrous cap seems to be artery-dependent. In the aorta and carotid artery, plaque ruptures occur with slightly thicker fibrous caps; the mean fibrous cap thickness of ruptured carotid plaques has been reported as 80 μm and that of ruptured aortic plaques as 130 μm.[87,88] This difference may reflect differences in vessel wall tension, being lowest in the coronary arteries, intermediate in carotid arteries, and highest in the aorta.

Thinning of the fibrous cap occurs by two concurrent and probably related mechanisms. One is the gradual loss of SMCs from the fibrous cap. Ruptured caps contain fewer SMCs and less collagen than intact caps,[89,90] and SMCs are usually absent at the actual site of rupture.[11,90] Because SMCs are the only cell type responsible for synthesizing the extracellular fibers of the fibrous cap, their loss inevitably leads to cap weakening. Death of plaque SMCs presumably occurs mainly by apoptosis, which takes place at an increased rate in advanced plaques,[91] and unlike the normal vessel wall, they are not replaced by local SMC proliferation.[92] This regeneration may be caused by cellular senescence.[93] Local SMCs have shortened telomeres and express multiple markers of senescence, and their proliferative index in vivo is very low.[91,93] In mice, which lack normal intimal SMCs, the fibrous cap forms by migration of cells from the vessel wall,[45,47] presumably from medial SMCs,[46] but whether replenishment of local, senescent cap SMCs in human atherosclerosis from neighboring proliferation-competent sources occurs is unknown.

At the same time, infiltrating macrophages degrade the collagen-rich cap matrix. Ruptured caps examined at autopsy are usually heavily infiltrated by macrophage foam cells,[11,79] which secrete proteolytic enzymes such as plasminogen activators and a number of matrix metalloproteinases (MMPs), including collagenases, gelatinases, and stromelysins.[12] MMPs are secreted in the form of latent zymogens that require extracellular activation, after which they are capable of degrading almost all components of the extracellular matrix. As a proof of principle, macrophages that overexpress a constitutively active mutant form of MMP-9 caused plaque ruptures in the apo E-deficient mouse model of atherosclerosis.[94]

Whether critical thinning of the fibrous cap takes decades to evolve or is much more dynamic is not known. However, the fact that fibroatheromas are commonly seen from 30 years of age,[34] when acute coronary syndromes are exceedingly rare, seems to indicate that the development of rupture-prone plaques usually is a slow, smoldering process.

Lipid-Rich Core. The presence of a lipid-rich core is the sine qua non of plaque rupture. If no lipid-rich core is present in the plaque, there is no overlying fibrous cap to rupture. However, a larger lipid-rich core also appears to confer greater risk than a small one.[17,95] The importance of lipid-rich core size for plaque stability is understandable, because the expansion of the lipid-rich core may erode the fibrous cap from below, and because the total lack of supporting collagen in the lipid-rich core confers greater tensile stress to the overlying fibrous cap. A large lipid-rich core may also promote thrombosis after plaque rupture and hence increase the risk of a clinical event because of high amounts of prothrombotic apoptotic microparticles and tissue factor within the core.[38]

Plaque Size. It has generally been thought that plaque size was not an important issue, but this concept more or less evolved out of the observation that stenosis has little predictive value for the occurrence of ACS, before the concept of remodeling was fully appreciated. Recently, an autopsy study has found that larger plaques are more frequently associated with rupture than small ones,[96] confirming an observation made by Yamagishi and associates in their prospective IVUS study.[97] However, plaque size is not an independent variable of plaque vulnerability because the size of ruptured plaques correlates positively with the relative size of the lipid core and inversely to the area of fibrosis.[96]

Severity of Stenosis. In autopsy studies, fatal thrombi have generally been considered to form in moderate to severely stenotic segments; but this is probably a result of the failure of past autopsy studies to account for the effect of remodeling because individual cross sections were studied. In retrospective angiographic studies, as many as 75% of all infarct-related coronary thrombi were precipitated by plaques that were not visible or only caused relatively modest luminal narrowing in a prior angiogram obtained weeks or months before.[76] The greater overall risk enforced by nonobstructive plaques can be accounted for in three ways.[81] First, nonobstructive plaques are much more prevalent than obstructive plaques. Second, expansive remodeling is correlated with other features of plaque vulnerability, such as the presence of a large lipid-rich core and thin fibrous cap.[61,62] Third, the thrombotic occlusion of an already severely stenotic segment may remain subclinical because of well-developed collateral blood flow.

Other Features. A number of additional plaque features are more commonly found in ruptured plaques than in intact plaques, including increased neovascularization and adventitial inflammation.[98,99] Furthermore, culprit lesions responsible for acute coronary syndromes are generally less calcified than plaques responsible for stable angina, and the pattern of plaque calcification also differs.[65] These features are not independently associated with plaque rupture, however, and if they are causally involved in plaque rupture, their most likely mode of action is through modulation of the thickness or inflammation of the fibrous cap or the size of the lipid-rich core. Their special importance, however, lies in the fact that they may be detected by noninvasive imaging.

Erosion-Prone Plaques

The processes that lead to coronary thrombosis without plaque rupture are unknown, and plaque erosion, being a diagnosis of exclusion, does not necessarily reflect a single pathogenesis. Although erosion (endothelial denudation) is generally present beneath the thrombus, this is not documented as the precipitating thrombogenic mechanism.

Focal or Multifocal Plaque Vulnerability

Often, multiple plaque ruptures and sometimes several luminal thrombi are present in ACS patients,[79,100,101] and the risk of a new coronary event caused by thrombosis on a nonculprit lesion is considerable during the following 12 months.[102] This indicates that patients may have simultaneous vulnerable plaque development in multiple sites of the coronary tree, with several plaque ruptures occurring within a relatively short period.

The number and distribution of vulnerable plaques are critical for choosing the most effective approach to treating them, localized or systemic. In two recent studies, the occurrence of TCFAs in the coronary tree, assumed to encompass the group of rupture-prone plaques, was examined. Cheruvu and coworkers[18] analyzed 14 hearts with at least one plaque rupture (average, 1.35 ruptures) and found a mean of 1.21 TCFAs at a second site. TCFAs were mostly located in the proximal part of the coronary tree, where most coronary thrombi also occur.[103] Mauriello and colleagues detected almost two TCFAs (in addition to the culprit plaque) in AMI

patients.[104] The true number of TCFAs in both studies was probably higher, however, because the applied sectioning of the coronary arteries was unlikely to reveal all TCFAs.

CONCLUSIONS

Clinical manifestations of atherosclerosis is a problem affecting middle-aged and older people, but atherosclerosis is a lifelong disease. Fatty streaks are present in most individuals after puberty, intermediate lesions in most from 20 to 30 years of age, and fibroatheromas are frequent in those aged 30 years and older.[14,15,34] It is unknown whether the plaques that form first in life are also the first to cause symptoms, but probably the plaque that eventually causes an ACS has a history that spans several decades before the event. Thus, there should hypothetically be ample time for prevention, but when in the lifetime of a plaque is it most effective to intervene? Most of our understanding of the molecular mechanisms of atherosclerosis relates to the development of atherosclerotic plaques. By comparison, our knowledge of what causes fibrous cap thinning and plaque rupture is much more incomplete, and the mechanism leading to thrombosis on eroded plaques is not known at all. Nonetheless, current approaches to primary prevention are predominantly focusing on high-risk middle-aged adults in whom advanced atherosclerosis is already present. It is likely, however, that slowing the development of atherosclerosis through dedicated primary prevention early in life would have a much more pronounced impact on clinical events later in life. Recent observations have suggested that a relatively small but lifelong reduction in the LDL level is much more effective than more profound lipid-lowering in older individuals who already have clinical evidence of atherosclerosis.[105]

When coronary atherosclerosis begins to cause symptoms, it is a widespread disease affecting most of the epicardial portion of the coronary arteries. In ACS, an invasive approach (e.g., percutaneous coronary intervention) may be needed to obtain rapid, complete, and sustained recanalization of the culprit artery, and the potential to prevent new events by local treatment of coexisting asymptomatic lesions assumed to be vulnerable is being explored. A target lesion approach alone, however, will not eliminate the threat posed by all the vulnerable plaques to come, and their overall risk determines the prognosis over the long term. Therefore, the key to prevention and treatment of atherosclerosis remains lifelong risk factor reduction through societal measures, individual lifestyle modifications, and systemic medical therapy in those at higher risk.

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CHAPTER 7

Molecular Mechanisms of the Acute Coronary Syndromes: The Roles of Inflammation and Immunity

Peter Libby

Histologic observations have taught us much regarding the pathophysiology of the acute coronary syndromes. Pathoanatomic examination of atheromas that provoke fatal thrombosis reveals much about the mechanisms of this extreme form of an acute coronary syndrome. Although previously controversial, the role of thrombosis in producing the acute coronary syndromes has now gained wide acceptance.

Four distinct microanatomic mechanisms can precipitate the acute coronary syndromes.[1,2] Plaque rupture, the most common and perhaps the best understood, causes two thirds to three quarters of fatal acute myocardial infarctions (Fig. 7-1A). Superficial erosion without a frank rupture in the plaque's fibrous cap underlies some 20% of fatal acute coronary thrombi (see Fig. 7-1B), and erosions around calcium nodules account for a few acute coronary thromboses. Another mechanism of rapid plaque expansion, intraplaque hemorrhage, may also play a role in precipitating some cases of acute coronary syndromes.

Beyond these structural microanatomic substrates, which usually involve a disruption of the plaque, functional changes can also influence the thrombotic potential and stability of clots. A balance between procoagulant and anticoagulant factors prevails at any particular moment in the vascular compartment (Fig. 7-2). Similarly, profibrinolytic and antifibrinolytic factors may regulate the stability of clots. In addition to fluctuations in the blood compartment in the determinants of thrombosis, local regulation at the level of the arterial wall in these regulatory pathways may determine the consequences of any given plaque disruption.

Recognition has increased that inflammation is a fundamental and common theme in the structural and functional pathways to thrombosis. Furthermore, molecules and cells involved in both the innate and adaptive arms of the immune response may participate in many of the processes that precipitate the acute coronary syndromes. These new insights aid in understanding the pathophysiology of the acute coronary syndromes; they have prognostic and therapeutic implications as well. This chapter describes recent advances in the pathophysiology of the acute coronary syndromes, emphasizing the practical clinical import of these new concepts.

MECHANISMS OF PLAQUE DISRUPTION

Plaque Rupture

Many human coronary atheromas contain a lipid-rich central core. In addition to extracellular lipid debris, the lipid core contains foamy macrophages, many of which have surfaces studded with the potent procoagulant, tissue factor.[3-5] A collagenous fibrous cap overlies the typical lipid core and serves as a barrier between the blood compartment, which contains proteins of the coagulation cascade, and thrombogenic material in the lipid core.

In plaque rupture, a thinned and friable fibrous cap fractures. The contact between blood and tissue factor in the lipid core unleashes the clotting cascade. Collagen uncovered during plaque disruption can promote platelet adherence and activation. Resistance of the fibrous cap to rupture depends largely on the integrity of the interstitial collagen in the extracellular matrix. Collagen fibrils lend biomechanical strength to the fibrous cap. In general, interstitial collagen has considerable stability and turns over slowly, if at all. Moreover, until recently, most regarded the atheroma as a metabolically inactive graveyard for excess cholesterol stuck in the artery wall. It is now understood that the atheroma teems with living cells whose functions and exchanged messages may dictate the clinical consequences of the atheromatous lesion. Inflammation has also emerged as a unifying concept in the pathogenesis of atherosclerosis and its complications.

Therefore, in the early 1990s, I hypothesized that the collagenous skeleton of the plaque depends on a dynamic balance between ongoing collagen synthesis and degradation.[6] The arterial smooth muscle

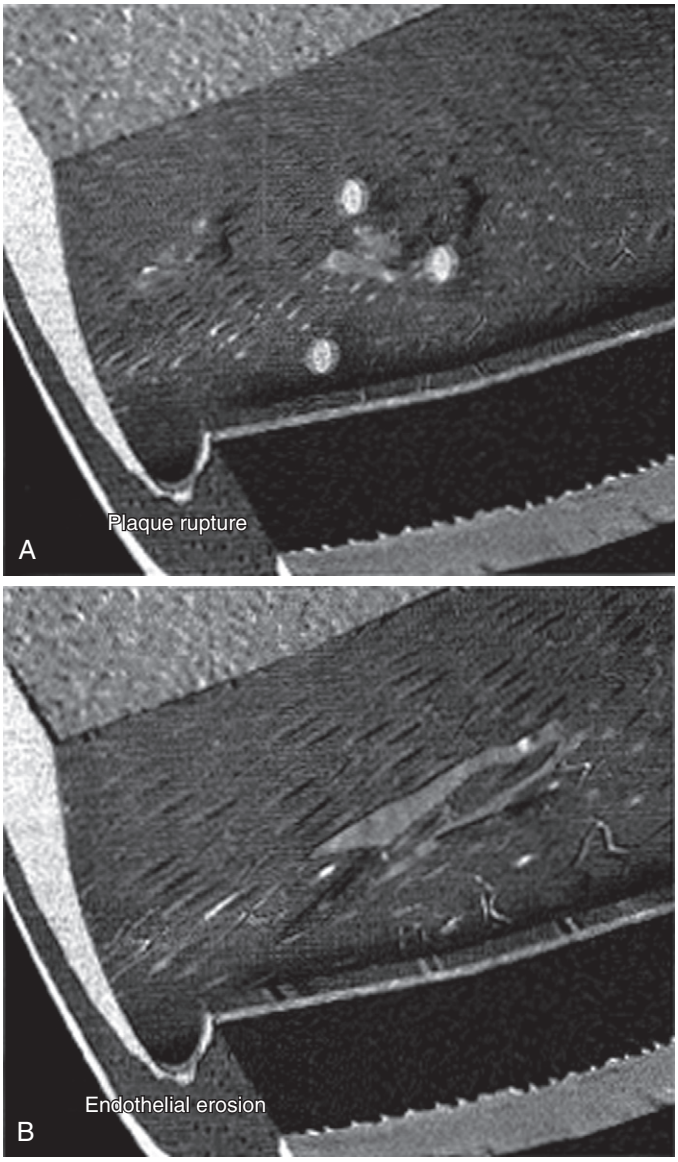

FIGURE 7–1 Depiction of a cross section of a coronary artery shows an intimal flap corresponding to a ruptured fibrous cap **(A)** or a patch of desquamating endothelial cells corresponding to superficial erosion **(B)**.

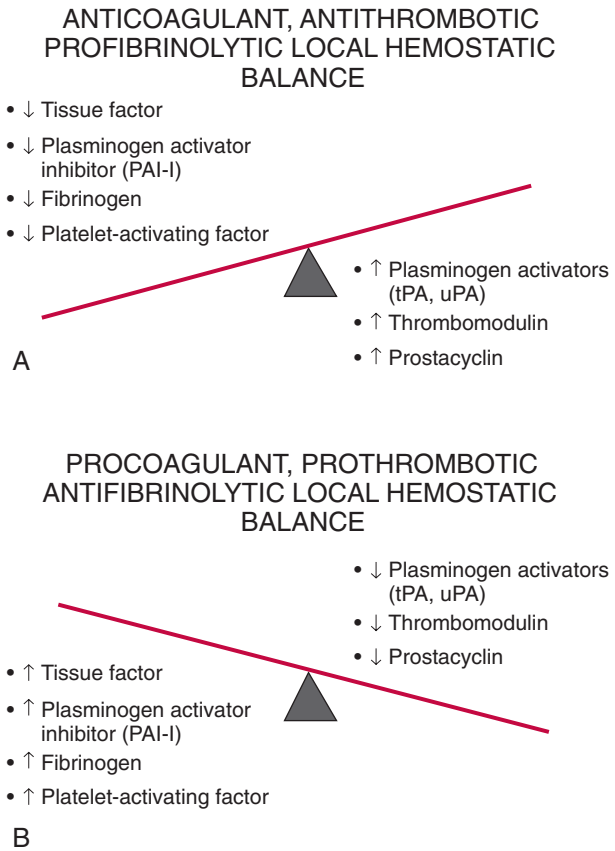

FIGURE 7–2 **A,** In the normal endothelium, anticoagulant, profibrinolytic, and antithrombotic molecules *(right)* outweigh the procoagulant antifibrinolytic factors *(left)*. **B,** In the activated, or dysfunctional, endothelium, the procoagulant, prothrombotic, and antifibrinolytic factors prevail, tipping the balance toward an environment that favors clot formation and stability. tPA, tissue type plasminogen activator; uPA, urokinase plasminogen activator.

cell synthesizes the great majority of the collagen in this structure, and expression of interstitial collagen genes by smooth muscle cells depends on the inflammatory milieu. Interferon-γ (IFN-γ), a cytokine produced in plaques, almost halts procollagen gene expression by cultured smooth muscle cells.[7] Atherosclerotic plaques contain IFN-γ. When activated, the T lymphocyte produces high levels of IFN-γ.

Other cells found in the atheroma can also elaborate IFN-γ under certain circumstances. For example, smooth muscle cells and macrophages exposed to a combination of cytokines found in the plaque (interleukin [IL]-12 and IL-18) can secrete IFN-γ.[8] These observations led to the hypothesis that T cells may locally inhibit collagen synthesis in regions of the atherosclerotic plaque. T lymphocytes localize in atherosclerotic plaques, particularly in the shoulder region, where tears in the plaque often cause rupture.[9] Indeed, computational analysis of the biomechanical forces impinging on a plaque reveal maxima in circumferential stresses at the shoulders of plaques.[10] Rekhter and colleagues[11] have painstakingly enumerated cell types in various regions of the plaque and simultaneously assessed rates of interstitial collagen gene expression by in situ hybridization. They found a highly significant coincidence of T cells within regions of lower levels of interstitial collagen gene expression. Van der Wal and associates[12] have carefully enumerated cell types at sites of actual disruptions of human coronary plaques that caused fatal thrombosis, and have found abundant T cells in the vicinity of the site of plaque disruption.

Taken together, these results indicate that IFN-γ derived from T cells in the shoulder region of inflamed plaques can impede the synthesis of new collagen by smooth muscle cells. Inhibition of interstitial collagen synthesis would interfere with the ability of the smooth muscle cell to repair and maintain the all-important fibrous cap. Experiments in mice rendered scorbutic by genetic engineering have shown that vitamin C (ascorbic acid) deficiency impairs the collagenous structure of the plaque.[13] Because vitamin C promotes the cross-linking of collagen chains, this finding supports a role for collagen protein production in determining the structure of the plaque's fibrous cap.[14]

Intact collagen fibrils resist degradation by all but a few enzymes, known as interstitial collagenases. Humans produce three interstitial collagenases. These three enzymes belong to a broader family of proteinases that are dependent on zinc atoms and are thus known as matrix metalloproteinases (MMPs).[15] In 1991, Henney and coworkers detected messenger RNA encoding one MMP-stromelysin, or MMP-3, in human atherosclerotic plaques.[16] Importantly, human atheromata also overexpress interstitial collagenases.[17,18] The interstitial collagenases (MMP-1, -8, and -13) localize with

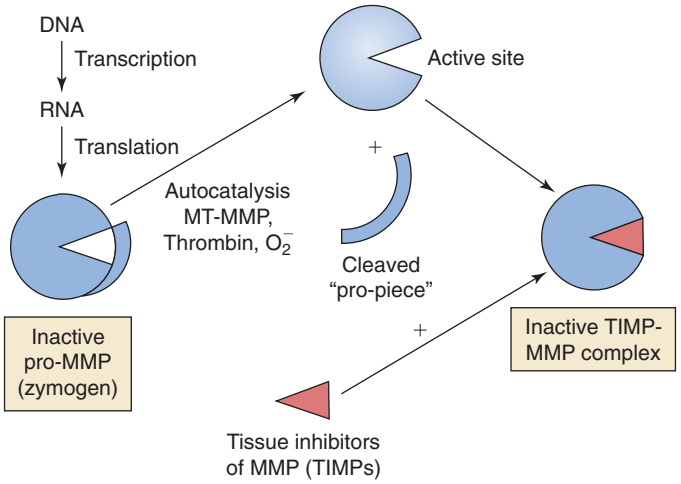

FIGURE 7–3 Multiple levels of control of activity of extracellular matrix metalloproteinases (MMPs). MMPs, first synthesized as inactive zymogen precursors, require processing to gain enzymatic activity. Cleavage of the "pro" portion of nascent protease can occur autocatalytically or heterocatalytically, involving other MMPs, including MT-MMP, thrombin, or reactive oxygen species in the case of MMP-2. Cleavage or unfolding of the pro portion of the molecule allows the active site of the enzyme to access substrates and degrade them. Ubiquitously distributed tissue inhibitors of MMPs (TIMPs 1-4) can bind to active protease, blocking the active site and rendering the enzyme inactive. Thus, control of MMP activity depends on gene transcription, translation, post-translational control of zymogen activation, and the balance between proteases and their endogenous inhibitors, TIMPs. *(Adapted from Libby P, Lee RT: Matrix matters. Circulation 2000;102:1874-1876.)*

macrophage foam cells and smooth muscle–derived foam cells in regions of human atherosclerotic plaques at sites particularly prone to rupture, as shown by biomechanical and pathologic studies.[19,20] Observations made on experimental atheroma in rabbits have shown the importance of the macrophage as a source of interstitial collagenase.[21,22] MMP-8 degrades type I collagen more efficiently than MMP-1 or MMP-13. Type I collagen accounts for the bulk of collagen in the atheroma. Therefore, MMP-8 has a substrate specificity that may render it one of the most important proteinases in degrading collagen in the atheroma. In other studies, Sukhova and colleagues[23] and Liu and associates[24] established overexpression of nonmetalloenzymes, including cathepsins S, K, and L, in the atherosclerotic plaque. Although chiefly implicated in elastolysis, cathepsin S may exhibit interstitial collagenase activity as well.

The overexpression of messenger RNA and protein corresponding to interstitial collagenases does not necessarily translate into increased enzyme activity. Proteinase cascades important in biologic control undergo regulation at several levels. MMPs, first synthesized as inactive precursors, require activation to attain their enzymatic function (Fig. 7-3). Moreover, widely distributed endogenous inhibitors can limit the action of any activated form of the MMPs. Four members of the tissue inhibitor of MMP (TIMP) family exist, and vascular lesions can contain all four.[15] Also, human arteries express tissue factor pathway inhibitor 2 (TIMP-2), which also inhibits collagenases.[25] This homologue of TIMP-2 actually inhibits tissue factor poorly but blocks the action of collagenases as potently as TIMPs. Even if active molecules of the interstitial collagenase were to exist in the plaque, they could not digest collagen unless they overpowered these endogenous inhibitors. Unfortunately, none of the available immunologic reagents can distinguish the inactive zymogen form of the interstitial collagenases from their active counterparts.

Thus, the mere presence of immunoreactive interstitial collagenases in plaques does not imply that they actively participate in collagenolysis in situ. To prove this point, our laboratory assessed collagen degradation directly in situ using an antibody that selectively recognizes collagen that has undergone cleavage by interstitial collagenase. This study established that active collagen breakdown occurred in advanced human atheromas and, further, colocalized MMP-1 and MMP-13 within regions of collagenolysis in situ.[19] These observations all suggest that enhanced breakdown of interstitial collagen caused by the action of MMPs may contribute to thinning and weakening of the fibrous cap and, hence, to the pathogenesis of plaque rupture. Therapies that limit the acute coronary syndromes may act in part by stabilizing plaques by interfering with collagen breakdown and increasing collagen synthesis. In rabbits with dietary or endogenous hyperlipidemia, lowering of cholesterol by dietary or pharmacologic means can reduce the expression of interstitial collagenase and promote collagen accumulation within plaques.[22,26,27]

Recent studies in mice have provided strong support for the concept that proteinases that can degrade the extracellular matrix can contribute to the collagen composition of plaques and their tendency to cause thrombosis.[28] Mice that bear a mutation that renders their interstitial collagen resistant to MMP collagenases in the context of genetically determined susceptibility to atherosclerosis have increased collagen accumulation in the atherosclerotic intima.[29] Atherosclerosis-susceptible mice altered genetically to lack a major murine interstitial collagenase, MMP-13, similarly show augmented collagen content in their atherosclerotic plaques.[30] Mice manipulated to lack another enzyme known as MMP-14 in cells derived from bone marrow also accumulate lesional collagen.[31] MMP-14 appears to act by proteolytically processing the zymogen form of the interstitial collagenase MMP-13 to its active form, rather than by attacking collagen directly.

Proteinases not notable for their interstitial collagenase activity may also promote thrombosis in experimental atherosclerotic plaques in mice. Atherosclerosis-susceptible mice infected with a virus that directs the expression of an activated form of the gelatinase MMP-9 have shown evidence of plaque disruption.[32] Mice that bear compound mutations in apolipoprotein E and Niemann-Pick C protein demonstrate thrombotic complications of atherosclerotic plaques as well.[33] The proteinase cathepsin K may contribute to this thrombotic phenotype.

Recent evidence also provides insight into the links among adaptive immunity, inflammation, and thrombotic complications of atheroma. Mice genetically altered to augment T cell activity (because of T-cell–directed expression of transforming growth factor beta [TGF-β] receptor 2) show highly inflamed plaques, reduced collagen integrity, and evidence of thrombosis.[34,35] These mice have decreased levels of lysyl oxidase, an enzyme important in collagen cross linking. They also demonstrate augmented expression of two matrix-degrading proteinases, MMP-13 and cathepsin S.

Given the principal role of the smooth muscle cell in collagen synthesis in the artery wall, the level of collagen in a plaque may depend on the number of smooth muscle cells. The regulation of collagen gene expression in smooth muscle cells varies with the prevailing mediator milieu. For example, platelet-derived growth factor and TGF-β, protein mediators released from platelets at sites of thrombosis but also produced by many other cells, augment interstitial collagen gene expression in human smooth muscle cells.[7] Thus smooth muscle cells, when present, promote plaque stability. Histopathologic observations have shown an inverse correlation

between smooth muscle cells and plaque ruptures—plaques that have ruptured have few smooth muscle cells.[1] Hence, I proposed that the smooth muscle cell was the "guardian of the integrity of the plaque's fibrous cap."[6] It is now recognized that smooth muscle cells in the plaque can die. Cell death may cause smooth muscle cells in atherosclerotic plaques to drop out, eventually making a plaque more vulnerable.

Smooth muscle cells within the plaque can die by several mechanisms, including apoptosis, or programmed cell death.[36] Smooth muscle cells exposed to proinflammatory mediators found in the atheroma can die by apoptosis. Notably, a combination of proinflammatory cytokines can promote smooth muscle cell apoptosis. The members of the surface-based cell death signaling dyad, Fas/Fas ligand, also operate in plaques. These observations strengthen the link between inflammation and impaired stability of the fibrous cap in human atheroma.

Superficial Erosion

Another form of physical disruption of the atherosclerotic plaque contributes to many coronary thromboses.[2] Superficial erosion, rather than a frank fissure, in the fibrous cap accounts for approximately one quarter to one third of fatal coronary thrombi. Superficial erosion appears more commonly than fibrous cap fracture in younger persons, women, and those with hypertriglyceridemia or diabetes. The molecular pathways underlying superficial erosion have received less attention than those regulating the friability of the fibrous cap. Not all experts agree on the degree to which inflammation participates in superficial erosion. Virmani and coworkers[2] have emphasized the bland, noninflammatory nature of sites of superficial erosion in human coronary arteries. The Amsterdam group has consistently found evidence for the coexistence of T cells and macrophages at sites of plaque disruption caused by superficial erosion and rupture of the cap.[12]

Although the underlying mechanisms remain speculative, some mechanistic commonality may exist between these two most common forms of plaque disruption. In superficial erosion, endothelial cells may detach because the connections that tether them to the underlying basement membrane loosen. Type IV collagen, the major type of collagen in the subendothelial basement membrane, may also undergo proteolytic degradation. In contrast with the fibrillar collagens that make up the plaque's fibrous cap, type IV collagen in the basement membrane does not form fibrils. Type IV collagen also can undergo catabolism by MMPs. However, instead of the interstitial collagenases, this nonfibrillar type of collagen undergoes degradation by MMP-2, a form of gelatinase. Like the other MMPs, MMP-2 requires activation from a zymogen precursor to cleave its substrate, type IV collagen. The cell surface–bound proteinase known as membrane-type MMP, or MT-MMP (MMP-14), participates in the activation of MMP-2. Proinflammatory cytokines and oxidized low-density lipoprotein can augment the expression by endothelial cells of the MT-1–MMP/MMP-14 that can activate MMP-2.[37] Moreover, reactive oxygen species released from vascular cells and infiltrating inflammatory cells in inflamed plaques can activate MMPs directly.[38] Thus, active degradation of the subendothelial basement membrane caused by the proteinases regulated by inflammation may promote endothelial desquamation. Such a scenario could provide one mechanism for superficial erosion as a source of coronary thrombi.

In addition, endothelial cells may detach because they die. As in the case of smooth muscle cells, endothelial cells can undergo death by apoptosis. Some inflammatory mediators encountered by endothelial cells may promote resistance to apoptosis, partially by inducing the antiapoptotic pathway involving nuclear factor kappa B (NF-κB). However, other proinflammatory stimuli may sensitize endothelial cells to programmed cell death. For example, hypochlorous acid, the product of the enzyme myeloperoxidase, can provoke endothelial cell apoptosis.[39] Macrophages in the human atheroma contain myeloperoxidase, and substantial evidence supports local generation of hypochlorous acid within atherosclerotic plaques. Thus, increased endothelial cell death, regulated in part by inflammatory mediators, may contribute to the pathogenesis of superficial erosion.

Erosion Caused by Calcium Nodules

Erosion caused by mineral collections, niduses of calcification, provides another route to coronary thrombosis. This mechanism accounts for only 4% to 7% of fatal coronary thromboses. Calcification in atherosclerotic plaques depends on tightly regulated biochemical processes.[40,41] Proteins such as osteopontin and bone morphogenetic proteins may regulate the accretion of calcium mineral in atheroma.[42] Just as the level of collagen in the plaque depends on the balance of synthesis and degradation, the level of calcium mineral depends on a similar balance. Bone morphogenetic protein likely enhances bony metaplasia in atherosclerotic plaques. On the other hand, macrophages may break down deposits of calcium. Indeed, macrophages in human atherosclerotic plaques can express some of the enzymes implicated in bone resorption by osteoclasts, including cathepsins S and K. Observations in mice with mutations that affect the number and function of macrophages have illustrated in vivo the importance of the catabolism of calcified tissue in atheroma. Specifically, mice lacking macrophage colony-stimulating factor, and thus unable to produce mature macrophages, show increased levels of calcium in experimentally produced atheroma.[43] These observations show how the degree of calcification in atheroma depends in part on inflammatory signaling within the lesion.[40]

Recent computational data have suggested that microscopic deposits of calcium mineral, well below the threshold of in vivo imaging, can augment circumferential stress and thus promote plaque rupture.[44,45] These findings have clinical significance because individuals with low levels of conary arterial calcium detectable by various imaging modalities might nonetheless have mechanically jeopardized plaques because of these microscopic foci of calcification. Specks of calcium as small as 10 μm in diameter can adversely affect the biomechanical properties of plaques. These microscopic calcified nodules might represent the remains of apoptotic cells within the atheroma.

Plaque Hemorrhage

Intraplaque hemorrhage with rapid lesion expansion may also precipitate the acute coronary syndromes. Many earlier pathologic studies viewed intraplaque hemorrhage as a major pathway to coronary thrombosis. However, later pathologic studies involving painstaking serial sectioning identified ruptures of the plaque's fibrous cap as the primary lesion, with blood collection within the atheroma often secondary.

The amount of microvessels in the plaque may influence its biology in several ways. In the same way that growth of tumors depends on the formation of new blood vessels, the progression of atheroma may depend in part on neovascularization. Experiments with inhibitors of angiogenesis have shown attenuated lesion formation in mice.[46] Atherosclerotic lesions express a number of angiogenic factors. For example, acidic fibroblast growth factor correlates with microvessel formation in plaques and colocalizes with inflammatory cells.[47] Vascular endothelial growth factor, basic fibroblast

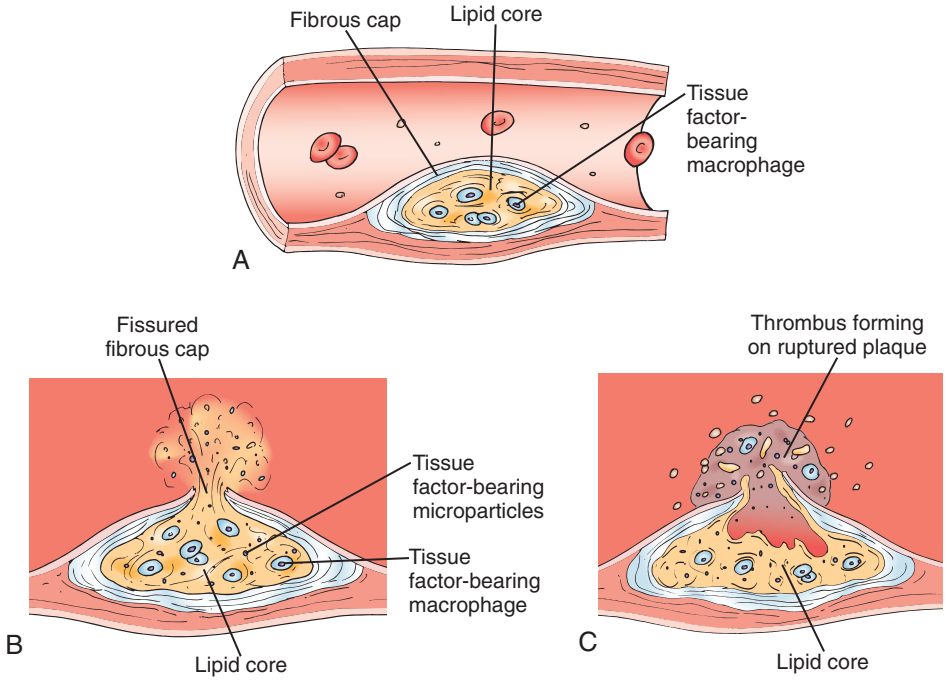

FIGURE 7–4 Depiction of the sequence of events in plaque rupture and thrombosis. **A,** The "vulnerable", or high-risk, atheroma has a thin fibrous cap overlying a large lipid core that contains tissue factor–bearing macrophages. **B,** When the fibrous cap fissures, tissue factor–bearing macrophages and microparticles become accessible to the coagulation proteins in blood. **C,** These events trigger thrombus formation on the ruptured plaque, which can lead to partial or transient coronary artery occlusion (clinically manifested as unstable angina) or a persistent and occlusive thrombus (leading to acute myocardial infarction).

growth factor, and other angiogenic proteins may promote plaque neovascularization.

Although intraplaque hemorrhage probably causes very few acute coronary syndromes by itself, the phenomenon may yet have important consequences for plaque evolution. Thrombosis in situ caused by ruptured friable neovessels in the plaque would lead to local thrombin generation. Thrombin potently stimulates smooth muscle cell migration, replication, and collagen synthesis.[48] In this manner, intraplaque hemorrhage might promote the evolution of fibrous atherosclerotic plaques. In addition, iron derived from hemosiderin in extravasated blood within the plaque may promote oxidative processes. Notably, the production of reactive oxygen species by the Fenton reaction requires transition metal cations, such as iron. The presence of microvessels within plaques and the potential role of intraplaque hemorrhage in lesion expansion and growth sound a cautionary note in the context of angiogenic therapy for myocardial ischemia. Administration of angiogenic growth factors in the regions of atherosclerotic plaques might actually enhance plaque neovascularization and favor intraplaque hemorrhage, with its attendant adverse consequences for plaque formation. If angiogenic therapy has a similar effect on the atheroma, plaque growth and instability could result from increased nourishment of ischemic myocardium.

REGULATION OF THROMBOSIS

Thus far, this discussion has centered on the mechanisms of plaque disruption. Such episodes permit the blood compartment to come into contact with thrombogenic materials. The consequences of a given plaque disruption, however, may depend on prevailing levels of proteins governing thrombosis in blood (see Fig. 7-2). Atherosclerotic events may correlate with levels of fibrinogen, the substrate of thrombin and the principal constituent of many intravascular thrombi. Fibrinogen, produced by the liver in response to systemic inflammation (the acute-phase response), may thus help determine whether a given plaque disruption leads to a sustained and propagated thrombus (Fig. 7-4). In addition, the levels of inhibitors of fibrinolysis, such as plasminogen activator inhibitor type 1 (PAI-1), can determine the operation of endogenous fibrinolytic pathways that combat the stability of thrombi. Elevated levels of PAI-1 in diabetic patients may partly explain their predilection to thrombosis.[49]

Coagulation depends not only on factors circulating in blood but also on local levels within the atherosclerotic lesion. For example, the amount of tissue factor in the core of a disrupted plaque may determine the degree of resultant thrombosis. Inflammatory mediators such as CD40 ligand increase the expression of tissue factor in plaques.[50] Inflammatory mediators regulate the antifibrinolytic balance in plaques as well.[49] Thus, inflammation regulates both the fluid phase and solid state factors that control thrombus formation. Therapies that reduce thrombotic complications of atherosclerosis—particularly lipid lowering and statins—may reduce events by decreasing thrombogenicity and increasing endogenous fibrinolysis. For example, dietary lipid lowering decreases tissue factor expression in rabbits.[51] Statins can decrease PAI-1 production by vascular cells and, under some circumstances, increase the production of plasminogen activators. The decrease in tissue factor noted with lipid lowering accompanies a decrease in the tissue factor inducer CD40 ligand and its receptor CD40.[51] In experimental atheroma, lipid lowering by statins can also decrease PAI-1 expression in situ.[52] Increasing evidence supports a link between thrombosis and inflammation.[48] Activated platelets exteriorize CD40 ligand and release it in a soluble form, in addition to other inflammatory mediators, including the recently

recognized myeloid-related protein (MRP)-8/14. Patients with acute coronary syndromes have elevated levels of MRP-8/14 as well as many other markers of inflammation (Fig. 7-5).[53] Importantly, platelets from individuals with acute coronary syndromes have elevated levels of the mRNA that encodes MRP-8. Platelets cannot transcribe new RNA because they lack nuclei; thus, the MRP-8 transcription reflects the patient milieu days before the onset of the acute coronary syndrome. This evidence furnishes strong support for a causal role of heightened inflammation in patients at short-term risk of acute coronary events. Plasma levels of MRP-8/14 predict higher recurrent event rates in survivors of acute coronary syndromes.[54]

CONCLUSIONS

Contemporary research has enabled a molecular approach to understanding the molecular bases of the acute coronary syndromes. Many pathways of evidence have converged on inflammatory processes as a unifying theme in the pathophysiology of the acute coronary syndromes. Proinflammatory mediators important in regulating these functions include proinflammatory cytokines, a major effector limb of innate immunity. However, much recent evidence indicates that the T lymphocyte may conduct the cytokine symphony in atherogenesis. Activated T cells localize to regions of plaque disruption and decreased collagen synthesis in situ. T cells produce high levels of CD40 ligand and IFN-γ, proinflammatory mediators of particular interest in the regulation of plaque stability and thrombosis. These observations indicate an important role for the pathways of adaptive, antigen-specific immunity in the pathogenesis of the acute coronary syndromes. Candidate antigens for stimulating an immune response during atherogenesis include oxidatively modified lipoprotein and heat shock proteins 60/65 expressed in stressed tissues, including atheroma, and by infectious organisms occasionally found in atheroma, such as *Chlamydia pneumoniae*.[9,55,56] β_2-Glycoprotein I, a target of antiphospholipid antibodies, may also play a role in autoimmunity during atherogenesis.[57]

These novel concepts of the molecular signaling involved in the acute coronary syndromes have enhanced our understanding of basic pathophysiology. More practically, the insight that inflammation is linked to coronary events has opened new avenues for risk stratification and prognostication. A consistent and rapidly accumulating body of evidence suggests that persons with signs of low-level inflammation are at heightened risk for future acute coronary events. Studies with the acute-phase reactant C-reactive protein and other markers of vascular cell activation, including MRP 8/14, IL-6, and soluble intercellular adhesion molecule 1, have shown that inflammation relates at several levels with future risk of atherosclerotic complications (Fig. 7-6).[58]

In addition to providing new tools for prognostication, the emerging molecular understanding of plaque thrombosis has therapeutic implications. The connections between inflammation and plaque stability have prompted experimental studies that shed new light onto the mechanisms whereby existing therapeutic strategies may effectively reduce thrombotic complications of atherosclerosis. Indeed, deploying statin therapy based on inflammatory status can limit acute coronary events and all-cause mortality.[59] Identification of novel targets by probing the molecular mechanisms of plaque disruption and thrombosis may also identify novel targets for therapy in the future. The emerging basic biology of the acute coronary syndromes may thus pave the way for novel therapies that will permit more effective reduction of the residual burden of atherosclerotic events.

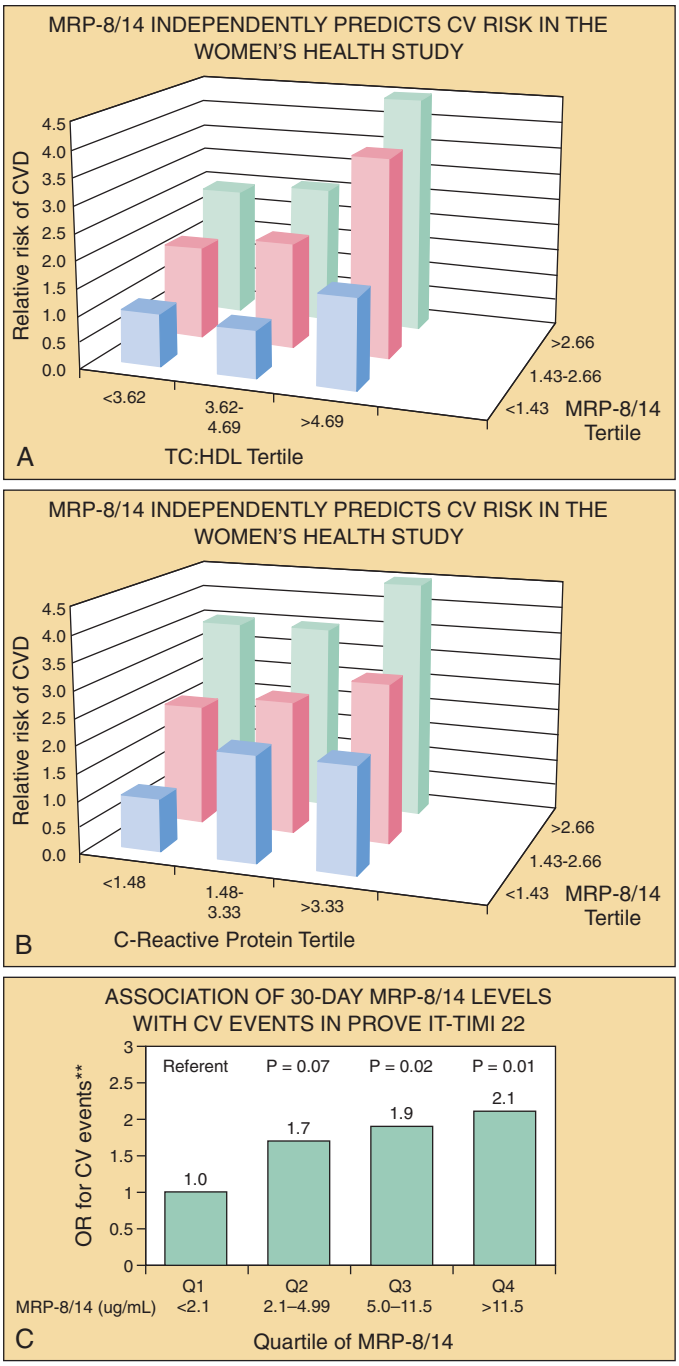

FIGURE 7–5 **A, B,** Relative risk of cardiovascular events for patients with acute coronary syndromes according to baseline levels of MRP-8/14 and the inflammatory markers high-density lipoprotein (HDL) or C-reactive protein (CRP). Taking MRP-8/14 levels (in μg/mL) into account improved risk prediction models over HDL or CRP (in mg/L) testing alone. **C,** Adjusted relative odds of cardiovascular (CV) death or myocardial infarction (MI) according to MRP-8/14 and high-sensitivity CRP (hsCRP). Patients with increased levels of MRP-8/14 and hsCRP had a 2.1-fold higher risk of CV death or MI (95% confidence interval [CI], 1.2-3.8) compared with those with low plasma concentrations of these biomarkers, after adjusting for qualifying syndrome, history of diabetes, history of hypertension, prior MI, heart failure, aspirin at discharge, achieved low-density lipoprotein (LDL) levels, and randomized treatment allocation. The low MRP-8/14, low hsCRP group included 128 patients; the low MRP-8/14, high hsCRP group, 108 patients; the high MRP-8/14, low hsCRP group, 97 patients; and the high MRP-8/14, high hsCRP group, 140 patients. CVD, cardiovascular disease. (***A, B*** *from Healy AM, Pickard MD, Pradhan AD, et al: Platelet expression profiling and clinical validation of myeloid-related protein-14 as a novel determinant of cardiovascular events. Circulation 2006;113:2278-2284;* ***C*** *from Morrow DA, Wang Y, Croce K, et al: Myeloid-related protein 8/14 and the risk of cardiovascular death or myocardial infarction after an acute coronary syndrome in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction [PROVE IT-TIMI 22] trial. Am Heart J 2008;155:49-55.)*

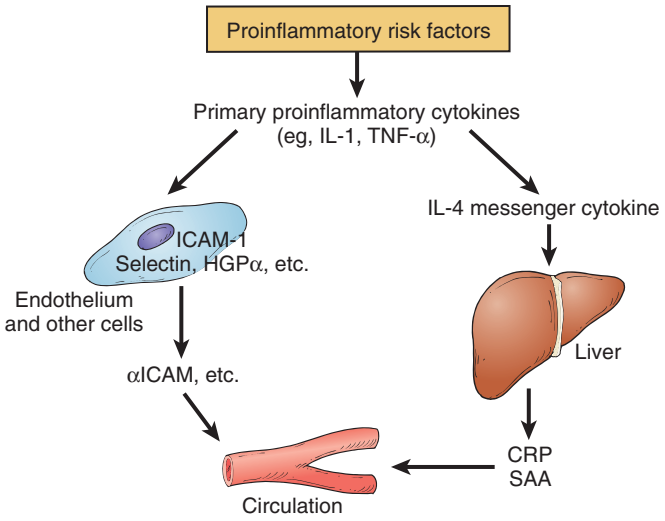

FIGURE 7–6 The pathway that generates inflammatory markers in the blood. Proinflammatory risk factors elicit the production of primary proinflammatory cytokines such as the soluble proteins interleukin-1 (IL-1) or tumor necrosis factor-alpha (TNF-α). These primary cytokines can stimulate production of IL-6, a messenger cytokine, from a variety of cell types, including vascular smooth muscle cells. IL-6 can change the program of hepatic protein synthesis from one that produces primarily housekeeping proteins (e.g., albumin) to one that favors production of acute-phase reactants such as C-reactive protein (CRP), serum amyloid-A (SAA), and fibrinogen (not shown). These soluble acute-phase reactants enter the bloodstream, where they can be sampled in venipuncture. The left side of this diagram depicts augmented expression of adhesion molecules such as the selectins or intercellular adhesion molecule 1 by endothelial and other cells in response to the primary proinflammatory cytokines.The adhesion molecules can be shed from the surface of the endothelial cell and enter the bloodstream, where they also can be sampled by venipuncture. In this way, the peripheral blood serves as a mirror of proinflammatory risk factors. *(From Libby P, Ridker PM: Novel inflammatory markers of coronary risk: Theory versus practice. Circulation 1999;100:1148-1150.)*

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CHAPTER 8

The Immune System in Acute Coronary Syndrome

Kuang-Yuh Chyu and Prediman K. Shah

ROLE OF IMMUNE SYSTEM IN ATHEROGENESIS

Atherosclerosis is a complex, chronic inflammatory disease of the arterial wall. Its underlying pathophysiologic mechanisms involve endothelial dysfunction, infiltration of atherogenic lipoproteins into the subendothelial layer with subsequent retention and oxidation, and activation of an immunoinflammatory gene program resulting in recruitment, retention, and activation of immunoinflammatory cells. The components of the immune system in the plaques include activated immune cells of both innate and adaptive immunity, immune-modulating cytokines, complement, and immunoglobulins.[1,2]

According to the classic paradigm, the immune system consists of innate and adaptive immunity.[3] Innate immunity is the first response to injury and offending organisms, does not require prior antigen exposure, and lacks immunologic memory. It is rapidly activated and relatively nonspecific. One of the important components of the innate immune response uses a small number of germline-encoded receptors, Toll-like receptors (TLRs), recognizing common molecular patterns shared by various infectious and noninfectious pathogens (pathogen-associated molecular patterns [PAMPs]). These PAMPs include lipopolysaccharides (LPSs) in gram-negative bacteria and unmethylated CpG DNA motif and lack immune memory. The innate immune response involves effector cells such as the macrophages, natural killer cells, mast cells, and natural antibodies produced by B-1 cells, which are a specific subset of B cells.[4-6] In contrast to innate immunity, adaptive immunity involves specific antigen exposure and recognition of highly specific epitopes, is slower to respond, and includes effector mechanisms such as T and B cells, antibodies, antibody-dependent cell-mediated cytotoxicity, cytokines, and chemokines. Although each type of immunity has its distinctive properties, such distinction is somewhat artificial because emerging experimental evidence indicates that innate and adaptive immunity are intricately linked and should be viewed as a continuum.[7]

Immune Responses

Both innate and adaptive immune responses have been shown to promote or inhibit atherosclerosis in experimental models, with likely parallel implications in human atherosclerosis.[8-11]

Atheropromoting Immune Response

Most of our knowledge of atherogenesis has been gained from observations in experimental animal studies. CD4+ T cells have been shown to play a pivotal role in atherogenesis. Activated CD4+ T cells and major histocompatibility complex (MHC)-II antigens are abundantly present in atherosclerotic plaques, suggesting their potential role in atherogenesis. Adoptive transfer of naïve CD4+ T cells or CD4+ T cells from malondialdehyde (MDA)–low-density lipoprotein (LDL) immunized donors into hypercholesterolemic immunodeficient mice results in an increase in atherosclerosis, further strengthening the notion that CD4+ T-cell–mediated adaptive immunity is proatherogenic.[12,13] In contrast, the role of CD8+ T cells in atherogenesis is currently unclear. Natural killer (NK) T cells, a subset of T cells bearing markers of NK cells, also participate in atherogenesis. NK T cells recognize lipid antigens presented by the class I–like molecule CD1d. Deficiency of CD1d molecule results in a reduction of atherogenesis, whereas activation of NK T cells via CD1d by α-galactosylceramide worsens atherosclerosis in experimental animals.[14-16] Adoptive transfer of NK T-cell–enriched splenocytes into immunodeficient, atherosclerosis-prone RAG1 (–/–)/LDL (–/–) mice resulted in increased atherogenesis when compared with the recipients transferred with NK T-cell–deficient splenocytes.[17]

TLRs are a group of pattern recognition receptors that orchestrate an innate proinflammatory immune response.[3]

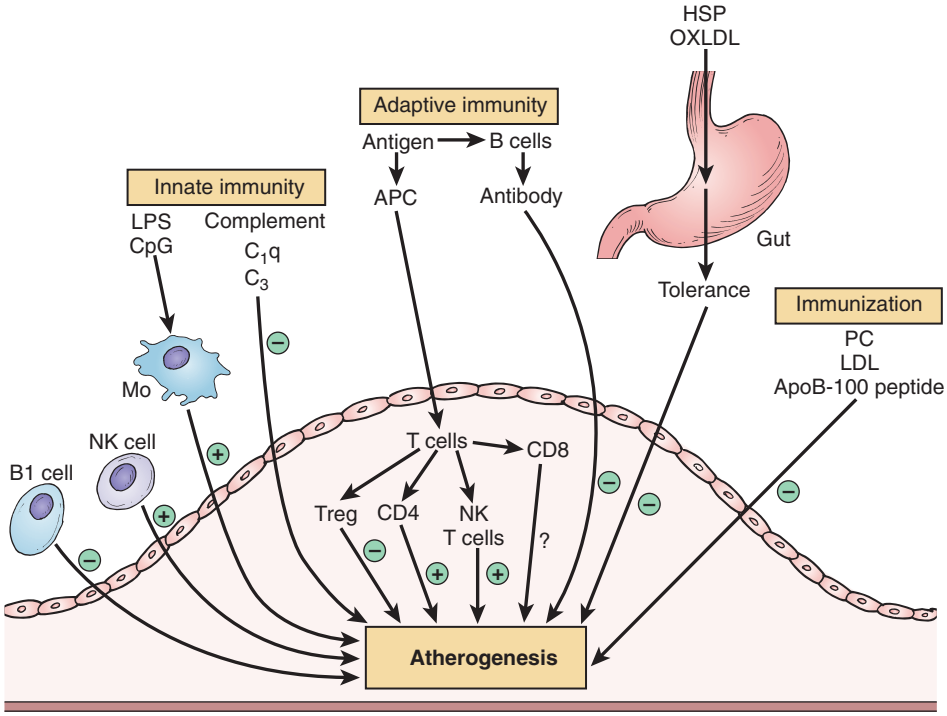

FIGURE 8-1 Various immune components and strategies that modulate atherogenesis. ⊕, enhancement; ⊖, reduction.

Macrophages and endothelial cells in murine and human atherosclerotic lesions express TLR4 and TLR2.[18,19] Genetic deletion of TLR4 or its downstream signaling adaptor molecule (myeloid differentiation factor 88, Myd-88) reduces atherosclerosis, plaque inflammation, and circulating inflammatory proteins in mice,[20,21] indicating the proatherogenic role of the TLR4- and Myd-88-mediated innate immune signaling pathway.

NK cells, another key component of innate immunity, are also present in atherosclerotic lesions.[22] Deficiency of functional NK cells significantly reduces atherosclerotic lesion size in experimental animals, further implicating innate immunity in proatherogenic effects.[23]

Atheroprotective Immune Response

There is abundant experimental evidence to support that certain aspects of the immune response have atheroprotective effects. Splenectomy has been shown to aggravate atherosclerotic lesions in apolipoprotein E (apo E) (–/–) mice; adoptive transfer of B cells from donor mice to splenectomized recipient ameliorates such increases in atherosclerosis. This establishes the atheroprotective role of splenic B cells in atherogenesis.[24] Such a role of B cells was confirmed by data showing that B-cell deficiency in LDL receptor (LDLR) (–/–) mice was associated with a reduced level of antioxidized LDL antibody and a concomitant increase in the aortic atherosclerotic lesion area.[25] A subset of CD4+ T cells that constitutively express CD25 is called regulatory T cells (Treg cells). These endogenous Treg cells are mostly produced by the normal thymus and are not induced from naïve T cells after antigen exposure in the periphery.[26] Their major function is to maintain immunologic self-tolerance actively by blocking T-cell activation in response to an antigen.[27] In experimental animals, deficiency of Treg cells has been shown to increase atherosclerosis, whereas promoting Treg cell function in vivo attenuates atherosclerosis.[28,29] It has been observed that the number of Treg cells and their ability to inhibit the proliferation of responder T cells were significantly hampered, respectively, in patients with acute coronary syndrome.

Activation of a humoral innate B-1 cell–mediated response to a phosphorylcholine head group exposed during LDL oxidation has been shown to reduce atherosclerosis in experimental models[30-32] further demonstrating the atheroprotective aspects of the immune system. A series of experimental studies has also shown that immunization with various LDL-related antigens (e.g., MDA-modified LDL, copper oxidized LDL, and apo B–related peptide epitopes) consistently reduces atherosclerosis in rabbits and mice.[8]

Taken these together, it is apparent that an individual immune component could be atherogenic or atheroprotective (Box 8-1 and Fig. 8-1). The overall atherogenic process is likely to be the result of complex interplay and balance among these individual components and other atherogenic risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, age, and cigarette smoking. Although information about the role of individual immune components in atherogenesis is increasing, their exact pathophysiologic role in acute coronary syndrome remains to be defined fully.

BOX 8-1 Effect of Different Immune Components on Atherogenesis

Immune Components Promoting Atherogenesis
CD4 T cells
NK T cells
NK cells
Toll-like receptor 4
Myd-88

Immune Components Reducing Atherogenesis
Spleen
B cells
Complement 3
CD4+/CD25+ T cells (regulatory T cells)

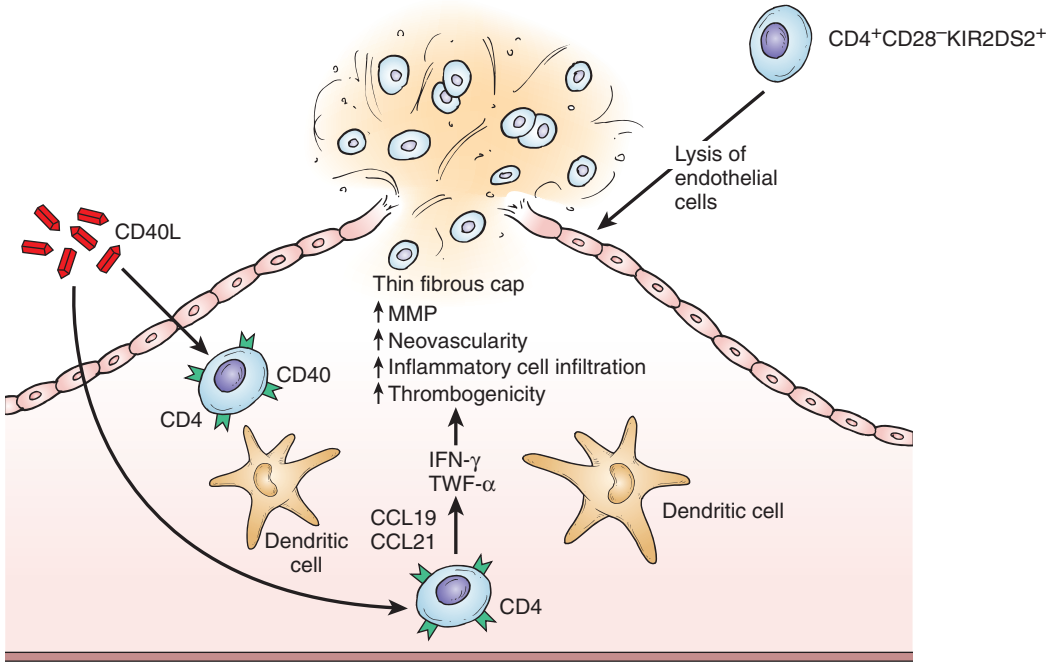

FIGURE 8-2 Activated immune components and their roles during acute coronary syndrome.

Evidence of Immune System Activation During Acute Coronary Syndrome

The hallmark of acute coronary syndrome is the disruption of an unstable atherosclerotic plaque leading to thrombosis superimposed on the plaque leading to critical coronary luminal obstruction (Fig. 8-2).[33] Rupture-prone vulnerable plaques contain a large lipid core with a thin fibrous cap, increased matrix-degrading metalloproteinases (MMPs), increased neovascularity, and inflammatory cell infiltration localized at the shoulder regions of the plaques in the thin collagen–depleted fibrous cap and in the adventitia.[34] Depletion of collagen from the fibrous cap, a prerequisite for plaque disruption, can result from excessive MMP-mediated collagen breakdown and/or depletion of collagen-synthesizing smooth muscle cells. Although the exact trigger for plaque rupture is not known, numerous observations have demonstrated that activated immune components exist in the unstable plaques. T cells, predominantly CD4+ T cells, and related cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are present more abundantly in unstable plaques when compared with stable plaques.[35] Such inflamed plaques contain higher amount of activated dendritic cells to produce T-cell recruiting chemokines (CCL19 and CCL21) and these dendritic cells colocalize with activated T cells.

These observations suggest that a lymphoid microenvironment exists in the inflamed plaques, allowing antigen presentation by the activated dendritic cells to T cells, with subsequent T-cell activation and secretion of inflammatory cytokines. These responses can lead to inhibition of smooth muscle cell function and survival, as well as activation of inflammatory cells (macrophages), leading to plaque instability. Also, patients with acute coronary syndrome, when compared with patients with stable angina or healthy controls, have a higher proportion of a specific subset of CD4+ T cells that are capable of inducing cell contact-dependent apoptosis of vascular smooth muscle cells, further contributing to plaque instability.[36]

In patients with unstable angina, there is also an alteration in the functional profile of circulating CD4+ T cells, with a bias toward IFN-γ production.[37] This bias leads to nuclear translocation of STAT-1 complexes and upregulation of the IFN-γ inducible genes *CD64* and *IP-10* in isolated circulating monocytes from patients with unstable angina, indicating activation of monocytes by IFN-γ.[38] These functionally altered CD4+ T cells lack the costimulatory molecule CD28 but have newly acquired immunoreceptors, including the killer immunoglobulin-like receptors KIR2DS2, NKG2D, and CX_3CR1. In patients with acute coronary syndrome, such CD4+/CD28– KIR2DS2+ T cells can lyse endothelial cells without antigen recognition.[39,40] Quantitatively, patients with unstable angina have a higher frequency of CD4+/CD28– peripheral T cells when compared with patients with stable angina. These T cells showed clonal expansion and shared T-cell receptor sequences in clones from different patients, suggesting stimulation by a common antigen. Such a monoclonal T-cell population can also be detected in the culprit but not in the nonculprit lesion of a patient with fatal myocardial infarction, suggesting the involvement of monoclonal T cells in plaque rupture.[41]

CD40 ligand (CD40L) is another protein expressed on activated CD4 T cells and platelets. It mediates many important effector functions of helper T cells[3] and drives inflammatory responses from the platelet-endothelium interaction. The circulating level of the soluble form of CD40L (sCD40L) is elevated in patients with acute coronary syndrome (ACS),[42,43] and higher levels of sCD40L in ACS patients predict a worse outcome.[44,45] Additionally, various statins have been shown to decrease the sCD40L level,[46-48] with an associated reduction of future adverse cardiovascular events, further supporting the role of sCD40L in acute coronary syndrome.

POTENTIAL ROLE OF IMMUNOMODULATION IN ATHEROSCLEROSIS TREATMENT

There is a considerable body of evidence suggesting a modulatory role of the immune system in experimental atherosclerosis and possibly in clinical atherothrombosis syndromes as well. These data suggest that immunomodulating therapies

may have a potential therapeutic role in atherothrombosis management. Statins have been used successfully to reduce atherosclerotic cardiovascular events. The primary mechanism responsible for such clinical benefit has been attributed to its lipid-lowering effect. However, in the past decade, experimental evidence has suggested that statins may also have immunomodulating effects. Statins have been shown to decrease the induction of MHC-II expression by IFN-γ and subsequent T-cell activation by human endothelial cells and monocyte-macrophages. Such repression of MHC-II expression is only specific for the inducible form of MHC-II but not for the constitutive MHC-II expression on professional antigen-presenting cells, such as B cells and dendritic cells.[49,50] Statin therapy has also been shown to reduce phagocytic activity and expression of CD40, CD83, CD86, and human leukocyte antigen (HLA)-DR on unstimulated and LPS-stimulated monocyte-derived dendritic cells and their ability to stimulate T-cell proliferation.[51] In patients with acute coronary syndrome, statin treatment was shown to reduce the frequency of CD4+/CD28– T lymphocytes[52] (see earlier for the significance of CD4+/CD28– null T-cells). In another study, rosuvastatin treatment was shown to decrease the circulating levels of IFN-γ, interleukin-6 (IL-6), and TNF-α and intracellular IFN-γ production in T cells in patients with acute coronary syndrome.[53,54] Although these immunomodulatory properties of statins may partially account for the observed clinical benefit in transplant patients and patients with autoimmune disease, their role of immunomodulating effects independent of lipid lowering in routine atherothrombosis prevention remains unclear.[55,56]

Many other immunomodulatory therapies are in preclinical testing, but most of them are aimed at the reduction of atherosclerosis and not specifically acute coronary syndrome. One interesting strategy is to use active or passive immunization to reduce atherogenesis. For an active immunization strategy, LDL (native or oxidized form), atherosclerotic plaque homogenate, and apo B-100–related peptides have all been used as immunogens for this purpose in various experimental animal models.[57] Although a reduction of atherosclerosis formation was observed in these studies, the exact underlying mechanisms are not clear. Passive immunization using an immunoglobulin G (IgG) preparation was also effective in reducing atherosclerosis experimentally; the effect was believed to be mediated via mechanisms such as Fc receptor blockade, neutralization of autoantibodies, or inactivation of T- or B-cell activities.[58,59]

Induction of tolerance is another immunomodulatory strategy that has been actively pursued experimentally to reduce atherosclerosis. Tolerance can be achieved by the clonal depletion of T cells or induction of CD4+/CD25+ T cells. Heat shock protein, β_2-glycoprotein I, and oxidized LDL are autoantigens that have been implicated in atherogenesis. Hypercholesterolemic mice that have been orally administered these antigens developed less atherosclerosis and reduced plaque inflammation.[60-63] However, successful application of one or more of these strategies awaits additional preclinical and clinical investigations.

CONCLUSIONS

Experimental evidence accumulated so far clearly indicates that the immune system, together with hyperlipidemia, hypertension, diabetes mellitus, age, and cigarette smoking, plays a vital role in atherogenesis and is active in acute coronary syndrome. Although most evidence is from preclinical studies, it still provides many valuable insights into understanding the potential mechanisms responsible for atherosclerosis and acute coronary syndrome. It is our hope that one or more of the immunomodulating strategies currently under investigation (Box 8-2) will find eventual applicability for atherothrombosis management in the clinical setting.

BOX 8-2 Immunomodulatory Strategies to Reduce Atherosclerosis*

Active Immunization Using These Immunogens
Native LDL
Oxidized LDL (ox-LDL)
ApoB-100–related peptides
Pneumococcus

Passive Immunization Using These Antibody Preparations
Human IgG preparation
Monoclonal mouse IgG2b against cardiolipin, native LDL, ox-LDL
Recombinant human IgG1 against apo B-100 peptide

Induction of Tolerance
HSP65
Ox-LDL
β_2-glycoprotein I

* Currently under investigation.

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CHAPTER 9

Myocardial Cell Death and Regeneration

Olivier Blanc-Brude

The mature mammalian heart can be represented as a four-chamber blood-pumping organ consisting of contractile cardiomyocytes and supportive stromal cells surrounded by fibrous connective tissue. After a period of intense cardiomyocyte proliferation and heart growth in the embryo, cell expansion and turnover become undetectable in the postnatal phase. Traditionally, the mature heart was thought to contain only a discrete number of quiescent cells (1 to 2×10^{10} cells/heart [average]), with little regenerative potential.[1] The heart maintains an average heart rate of 70 beats/min throughout an individual's life span. Noncardiomyocytes make up 75% of the total number of cells in the heart and only 25% of the total cell volume. The ratio of number of capillaries that provide oxygen and nutrients per cardiomyocyte is 1:1. In a setting of slow cell turnover and little regenerative potential, dysregulated or accelerated cell death under a pathophysiologic stress can rapidly lead to cell depletion, loss of function, and heart failure.

Although the overall cardiomyocyte population declines with age, proliferating cardiomyocytes have been recognized in normal adult hearts.[2,3] Their exact biologic significance remains uncertain. Evidence suggests that cardiomyocytes may not be quiescent terminally differentiated cells, but cells that respond to the modern cell biology concepts of proliferation, death, and ongoing turnover throughout adulthood.[4]

TYPES OF CELL DEATH

Necrosis and Apoptosis

Myocardial infarction causes cardiomyocyte death by ischemia that results from an imbalance between myocardial supply and demand of oxygen and nutrients. Necrosis, oncosis, and apoptosis are alternative mechanisms for demise. Strictly speaking, the term *necrosis* encompasses most terminal changes occurring in cell death, and oncosis is defined by cell swelling and karyolysis. This type of death is not governed by genetic regulation but is the consequence of biochemical insults and mechanical constraints that destroy essential cellular structures, mainly because of failure of membrane ionic pumps, resulting in cell swelling and rupture, inflammation, and tissue repair.[5] Exudative inflammation follows as dying cells release toxic contents in tissues before being ingested by phagocytes.[6] On the other hand, apoptosis is characterized by cell contraction and cell shrinkage and karyorrhexis. This type of death is genetically programmed and tightly regulated by a number of extra- and intracellular biochemical signaling pathways. Apoptotic cells are simply eliminated, without an inflammatory context and without compromising the survival of neighboring cells. There is strong interest in determining whether the prominent cardiac cell death seen after myocardial infarction (MI) occurs through regulated apoptotic reactions or indiscriminate necrosis. The former is believed to be an important mechanism; the latter is a key to the development of MI and its impact on subsequent cardiac remodeling and function.

Autophagy

The mechanisms for the degradation of mitochondria, other cytoplasmic organelles, and bulk proteins are under strict genetic control, referred to as autophagy or macroautophagy. Autophagy is characterized by the formation of double-membrane–lined vacuoles, known as autophagosomes, that merge with lysosomes to degrade their contents. Tagging with the ubiquitin peptide directs these cell constituents toward autophagosomes.[7] The process is controlled by specific genes, such as the ATG gene family and beclin-1, which control the assembly and function of autophagosomes.[8] Moderate and controlled autophagy ensures proper function and recycling of cell organelles,[9] and promotes increased cardiomyocyte survival.[10] Upregulation of autophagy by the overexpression of beclin-1 can be cardioprotective against ischemia/reperfusion (I/R) injury.[11] On the other hand, the

dysregulation of autophagy produces excessive ubiquitination of intracellular proteins or insufficient or inadequate lysosomal proteolytic activity. This leads to the absence of autophagosomes and accumulation of ubiquitinated proteins within the cell or to excessive destruction of essential organelles; both situations cause irreversible cell injury and death. Cardiomyocyte autophagy is activated in cardiac ischemia and further enhanced by reperfusion.[12] Autophagosomes are found in apoptotic and necrotic cells of chronic ischemic hearts,[13] and are seen as putative triggers for programmed cardiomyocyte death.[8]

Cardiac Regeneration

Of the total cardiomyocyte population, 0.0014% are in a mitotic state in resting adult hearts, 0.015% in remodeling failing hearts, and up to 0.08% in the proliferative zones surrounding areas of recent infarcts.[2,3,15] In a model of high cardiac cell turnover in transgenic mice expressing green fluorescent protein, up to 18.5% of cells adjacent to the infarct area and 7.5% of distal cells were mitotic in the first 3 months following coronary occlusion.[14] Thus, I/R appears to be associated with some spontaneous cell renewal; the exact nature of these proliferating cells, however, is uncertain and they can be invasive inflammatory cells, cardiomyocytes, or stromal cells.

Hypoxic cardiomyocytes activate the hypoxia-inducible transcription factors (HIFs) that sense oxygen depletion and regulate emergency expression of antiapoptotic genes.[15] Cardiac HIF-1α and HIF-2α strongly colocalize with markers of cardiomyocyte proliferation[16]; heterozygous transgenic mice partially deficient in HIF-1α, however, do not respond to ischemic preconditioning. Hence, cardiomyocyte HIF-1α is a key element for cell survival during ischemia, without necessarily protecting cardiac function completely.

It was demonstrated for the first time in 2003 that cardiomyocytes can originate from resident progenitor cell populations nested in specific zones of adult hearts, known as niches.[17-19] These cells are now believed to possess significant proliferative capacity to mediate cardiomyocyte turnover.[20-22] By contrast, bone marrow transplantation and other experimental studies have shown that relatively few progenitor cells have the potential to move from distal organs to repopulate injured or transplanted hearts.[23,24] Thus, cardiac proliferation may primarily consist of an expansion of resident cardiomyocyte progenitor cells. Whatever their sources and numbers, they are either insufficient or inappropriate in numbers to ensure spontaneous cardiomyocyte turnover and to compensate for the subsequent events of inflammation, apoptosis, tissue repair, and remodeling that result in an inert scar in place of contractile tissue.

Cardiac Death and Clinical Objectives

The current main drivers of treatment of MI are to open the artery and restore blood flow to prevent cardiac cell death, minimize infarct size, and maintain cardiac function. These measures are often ineffective or insufficient, fueling strong interest in novel cell therapies. Because the intrinsic proliferative capacity of mature adult cardiomyocytes does not allow sufficient or timely regeneration, alternative options are being tested, such as enhancing cardiomyocyte survival and/or replenishing contractile cells within the lesion. Cytoprotective approaches envisioned are further acceleration of reperfusion therapy, pharmacologic blockage of cell death, and artificial reintroduction of cells. Adding pharmacologic antiapoptotic therapy based on the knowledge of the timing, spatial distribution, and resolution of apoptotic reactions could help optimize therapeutic benefits.

CARDIOMYOCYTE DEATH IN THE ISCHEMIC AND REPERFUSED HEART

Ischemia and Cardiac Death

Cardiac cell death occurs rapidly on MI in response to a number of stimuli, which include hypoxemia and energy depletion in the absence of aerobic reserve, reoxygenation, acidosis, oxidative stress, and cytokine stimulation. The schedule of events leading to death has been described in patients and in animal models.[25-29] Diastolic and systolic dysfunction appear within 30 to 45 seconds of flow deprivation, followed by electrocardiographic changes; necrosis detected by sarcolemmal disruption appears within 30 to 40 minutes and cell death subsequently progresses exponentially, in a process initially described by Reimer and Jennings[29a] as "the wavefront phenomenon of myocardial death." In the absence of reperfusion or significant collateral flow, necrosis involves almost all the area at risk after 6 hours of occlusion and severe ischemia (Fig. 9-1).

Cardiomyocyte Death: Oncosis and Apoptosis

Oncosis is a form of cell death defined initially on histopathological bases and relevant to cardiomyocytes. It can be activated in three different ways: (1) damage to cell membranes, resulting in a loss of selective permeability, which contributes to the membrane attack complex (MAC) of the complement pathway; (2) membrane phospholipids degradation via dysregulated phospholipase activity or peroxidation by radical oxygen species (ROS); and (3) disruption of the respiratory chain machinery in mitochondria and a decrease in oxidative phosphorylation and the generation of adenosine triphosphate (ATP).[1,30] These events trigger sharp rises in intracellular Ca^{2+} concentration, followed by uncontrolled influx of extracellular water and ions, gradual cell swelling, and rupture.[31]

Apoptosis is identified by a number of unique modifications, including chromatin condensation and nuclear shrinkage, DNA fragmentation by endogenous nucleases, minor modifications of cytoplasmic organelles, plasma membrane blebs, and apoptotic bodies.[32] In a normal state, apoptotic cells do not exceed 0.002% of the total cardiomyocytes population; following MI, it is as high as 0.08% to 0.25% in the infarct area for weeks.[26,28,33,34] With the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) method, and internucleosomal fragmentation by agarose gel electrophoresis (200 base pair fragments), apoptosis is mainly detected in the border zone of histologically identified infarcts. Others have claimed that apoptosis is the major form of cardiomyocyte death, peaking as early as 4 to 5 hours after ischemia, with oncosis representing only 1 of 30 dead cells at this stage.[27] However, some necrotic cardiomyocytes exhibiting DNA fragmentation do not show additional features of apoptosis,[35] suggesting that true identification of apoptosis in MI could require not one but a combination of characteristics. Some cardiomyocytes associated with DNA nick-end labeling may actually reflect a state of DNA repair,[36,37] or apoptosis in stromal cells. The relative importance of apoptosis versus oncosis in MI remains unknown.[38-40]

Border Zone Apoptosis

Inflammation triggers intense myofibroblast proliferation and angiogenesis in the infarct area, which results in a vascularized granulation tissue relatively rich in cells within 4 to 6 days after the infarction. During this phase of tissue repair, cardiac cells still undergo apoptosis at the edge of the

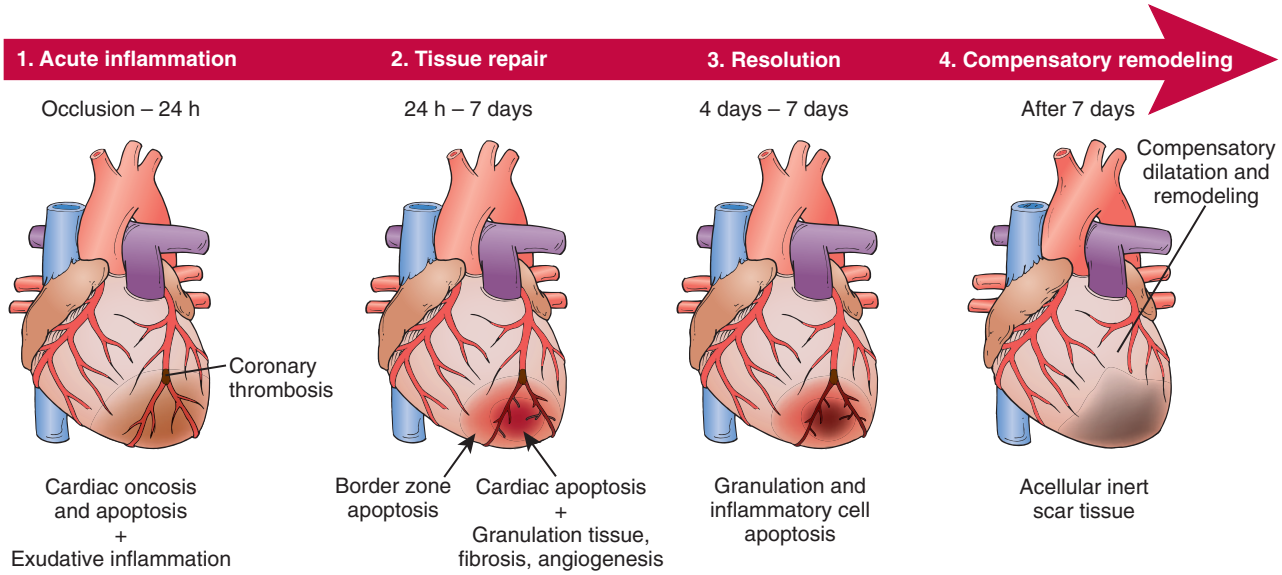

FIGURE 9–1 Cell death in acute myocardial infarction. Myocardial infarction triggers a healing response that progresses through various steps. **1,** Coronary occlusion induces myocardial ischemia that rapidly develops into cardiomyocyte death via oncotic and apoptotic pathways. Cell death triggers a burst of acute exudative inflammation, with neutrophil and monocyte invasion. **2,** Acute inflammation develops into a complex regulated process that orchestrates tissue repair via the activation of supportive stromal cells, including fibroblasts and endothelial cells. The development of vascularized granulation tissue is contained within the infarct area by apoptotic reactions that occur in the border zone in the periphery of the lesion. **3,** Inflammatory reactions gradually resolve and granulation tissue matures into collagenous scar tissue. Leukocytes, fibroblasts, and vascular cells undergo apoptosis. **4,** The resulting acellular scar is devoid of contractile function. Changes in biophysical constraints on the myocardial wall may lead to compensatory dilation and remodeling of the left ventricle.

histologically defined infarct area, as seen by caspase-3 activity, TUNEL labeling, and DNA laddering. This infarct border zone can account for up to 40% of the area at risk.[41] High concentrations of thrombospondin-1 (TSP-1), a potent anti-angiogenic agent and trigger of endothelial apoptosis, are seen within this zone,[42,43] suggesting that TSP-1 and apoptosis may serve as a barrier to the expansion of granulation tissue.[43] In addition, TSP-1 facilitates the expression and activation of transforming growth factor beta 1 (TGF-β1),[44] which exerts anti-inflammatory and antimitotic effects on multiple cells to contain the fibroproliferative reactions. Border zone apoptosis can thus be seen as cardioprotective.

Impact of Reperfusion

Whereas numerous cardioprotective methods have been described (see Chapter 25 for details), rapid restoration of blood flow is the ultimate requirement to confine ischemic cardiac death. Aggressive recanalization of coronary arteries is believed to represent the best approach for protecting cardiomyocytes. Fibrinolytic therapy and, whenever possible, primary angioplasty, are applied as promptly as possible. The window of opportunity for cardiomyocyte salvage lies within the first 3 hours after the coronary occlusion and may extend up to 12 hours.[45] Despite its overall cardioprotective effects resulting in a reduction of mortality, rapid interventional recanalization of coronary vessels induces counterreactions. Reperfusion can accelerate exudative inflammation and death of surviving cardiomyocytes.[46,47] TUNEL-labeled apoptotic cardiac cells accounted for approximately 4% of dead cardiomyocytes and necrosis for 40%, in patients 30 minutes after I/R injury,[48] and 6% and 12% after 2 to 4 hours of ischemia reperfusion, respectively.

Membrane phosphatidylserine (PS) externalization is considered one of the earliest markers of apoptosis. It is caused by a loss of membrane phospholipid symmetry, with PS accumulating on the outer surface of the membrane. Recombinant annexin V has a strong specific affinity for PS and is used as a marker of PS exposure.[49] TUNEL-positive nuclei cardiomyocytes with intact plasma membranes are also seen in the I/R area complicating the interpretation of quantitative data.[35] Late recanalization in the subacute stages between 4 days and 2 weeks after MI is associated with less cardiac apoptosis and remodeling than recanalization during the acute phase, providing an experimental basis for delayed revascularization.

CARDIAC DEATH AND ACUTE-PHASE INFLAMMATION

Inflammatory Cell Invasion

Myocardial necrosis is associated with exudative inflammation and tissue invasion by neutrophils and monocytes-macrophages.[50] Ischemia induces the release of interleukin-1 (IL-1), interferon-γ (IFN-γ), IL-8, and tumor necrosis factor-α (TNF-α); the latter two are potent chemoattractants for neutrophils. Chemokines are a family of highly basic small proteins with a conserved tridimensional structure.[51] IL-8 and lipopolysaccharide-induced CXC chemokine (LIX) are potent chemoattractive chemokines of the cysteine-X–cysteine ligand (CXCL) subgroup, and appear to mediate neutrophil invasion.[52] Other chemokines of the cysteine-cysteine ligand (CCL) subgroup, such as macrophage chemoattractant protein-1 (MCP-1), MCP-3, and macrophage inflammatory protein-1α and -1β (MIP-1α and MIP-1β) are upregulated without influencing infarct size and angiogenesis but with delayed inflammatory cell recruitment and tissue repair, resulting in less remodeling. Genetic deletion of the main MCP-1 receptor, CCR2, causes a partially similar phenotype

of delayed inflammatory cell invasion and reduced remodeling.[53] Both CC and CXC play a major role in the rapid recruitment of leukocytes after MI. Activation of the complement cascade was also observed during acute cardiac injury.[54,55] The complement cascade is activated through the classic, alternative, and lectin pathways,[56] and dying cardiomyocytes release complement-activating moieties. The potent anaphylatoxin C5 is specifically activated to recruit neutrophils within the first hour of ischemia and activates terminal complement pathways.[57] Reperfusion triggers further increases in IL-8 and TNF-α complement activation and excessive inflammatory reactions.[58] In the rabbit model, specific inhibition of activated protein C1[59] or the anaphylatoxins C3a and C5a by the soluble complement receptor type 1[60] results in a strong reduction in exudative inflammation. The complement MAC triggers oncosis in multiple cell types, including cardiomyocytes and endothelial cells, leading to local vascular injury. Despite all these cues, clinical trials with a C5-neutralizing antibody in patients with acute MI has failed to demonstrate improvements in infarct size or cardiac function.[61]

Inflammation and Cell Death

Acute exudative inflammation generates a strong burst of ROS generation, increases nitric oxide (NO) release and the secretion of pro- and anti-inflammatory cytokines that profoundly modify the ischemic environment. These moieties also influence cardiomyocyte function and survival.

Reactive Oxygen Species

Superoxide secreted by neutrophils and from other sources and other ROS are highly reactive biochemical moieties that react and modify lipids, proteins, and DNA to cause cell damage and death. At rest, the toxic reactive species are neutralized by enzymatic reactions involving superoxide dismutases (SODs), catalase, or glutathione peroxidase. These enzymes, however, are overwhelmed by the ROS burst generated in MI. ROS activate the Na^+/H^+ exchanger isoform 1 (NHE1), which mediates cytochrome C release into the cytosol, activation of caspase-3, and DNA degradation.[62] NHE1 is phosphorylated and activated by p90 ribosomal S6 kinase (RSK).[63] Transgenic mice with cardiac-specific overexpression of dominant negative p90 RSK displayed a 40% reduction in apoptosis on I/R injury. I/R and H_2O_2 also decreased the expression of antiapoptotic proteins and sensitized cardiomyocytes to Fas-mediated apoptosis.[64] Transgenic mice overexpressing superoxide dismutase (SOD) 1[65] or manganese SOD[66] have smaller infarct sizes than littermates. The combined administration of recombinant SOD and catalase reduces infarct size in I/R injury in dogs,[67] when administered immediately prior to ischemia or within minutes after reperfusion, situations that are rarely encountered in clinical practice. Inhibition of the Na^+/H^+ exchanger with cariporide failed to benefit patients experiencing acute MI or undergoing coronary artery bypass grafting (CABG).[68]

Toll-like receptors (TLRs) are a family of 12 cell surface effectors in innate immunity that mediate the recognition of molecular patterns associated with pathology. TLRs are activated by ROS, extracellular matrix fragments, microbacterial components, including lipopolysaccharides, and many other moieties from damaged tissues. TLR-4 is strongly upregulated in infarcted mouse hearts and human cardiomyopathic hearts.[69] Cardiomyocyte apoptosis is downregulated[70] and infarct area is halved after I/R injury in transgenic mice lacking TLR-4.[71] In contrast, TLR-2–deficient mice displayed similar infarct sizes and inflammatory cell invasion after MI, but reduced long-term remodeling.[72] In vitro, the activation of TLR-2 by ROS[73] and of TLR-4 by lipopolysaccharide reduced death in cultured cardiomyocytes via adaptor protein MyD88[74] and IL-1 receptor–associated kinase.[75] Hence, ROS, TLR-2, and TLR-4 may have diverse effects on cardiomyocytes. The nature of TLRs' contribution to cell death during MI remains to be clarified.

Nitric Oxide

Nitric oxide synthases (NOSs) form a group of three enzymes, NOS1 (neuronal NOS), NOS2 (inducible NOS), and NOS3 (endothelial NOS), which catalyze the conversion of L-arginine to L-citrulline and nitric oxide (NO). NO is a multipotent mediator that can promote death or survival, depending on its concentration and mechanism of production.[76] NOS2 increases significantly in 48-hour-old infarcts coinciding with inflammatory cell invasion, and persists for up to 14 days. In vitro, the combination of neutrophil and macrophage cytokines TNF-α, IL-1β, and IFN-γ triggers cardiomyocyte NOS2 expression and the generation of large amounts of NO.[77] Selective NOS2 inhibition in infarcted hearts decreases inflammation and improves recovery, supporting the concept that excess NO produced by inflammatory cells is noxious for cardiomyocytes and tissue injury.[78] NO produced by NOS2 activity further downregulates the expression of the antiapoptotic protein, stimulates Bax, and induces apoptosis in MI.[79] Excessive NO triggers mitochondrial permeability transition (MPT) pore opening and cytochrome C release and initiates caspase-activation.[80] NO can react with ROS to form peroxinitrite, which reacts with proteins, lipids, and nucleic acids, modifies the redox (reduction-oxidation) potential of the intracellular environment and promotes apoptosis.[81] More specifically, NO and peroxinitrite inhibit SOD activity and enhance superoxide accumulation and cell damage. On the other hand, NO produced in normal conditions via basal NOS1 and NOS2 activity may be protective against cardiomyocyte apoptosis and inflammatory invasion.[82] NO also upregulates Bcl-2 expression and blocks caspase-3 activation.[83] NOS3 is expressed in cardiomyocytes and cardiac endothelium, where it mediates large-vessel vasodilation, inflammatory cell recruitment, and angiogenesis. NOS3-deficient mice display larger infarcts after MI[84] and I/R.[85,86] This is consistent with the direct and indirect roles of NO in cardiomyocyte survival and angiogenesis after MI, in delayed cardioprotection after ischemia- and anesthetic-induced preconditioning, and increased inflammation and larger infarct size after I/R in NOS2-deficient mice.[87] The ultimate influence of NO on cardiac death may thus depend on the local levels of ROS, as well as the timing and intensity of its release.

Proinflammatory Cytokines

Proinflammatory cytokines secreted by neutrophils and macrophages (TNF-α, IFN-γ, IL-1) contribute to cell death in ischemic hearts. IL-1 and TNF-α are early inflammatory cytokines released after MI. TNF-α is upregulated in human cardiac infarcts, with levels reaching peak values after 5 to 7 days, which correlates with increased caspase-8 activity and cardiomyocyte apoptosis.[88] Cardiac death contributes to complement cascade activation, ROS generation, and local TNF-α release, which upregulates the secretion of multiple cytokines. Cardiomyocytes are insensitive to physiologic levels of TNF-α, but high concentrations enhance the cardiomyocyte expression of proapoptotic Fas ligand (FasL) and Bim[89] and accelerated Fas-mediated apoptosis.[90-92] TNF-α can also stimulate the apoptosis of endothelial cells[93] and has deleterious effects on the vasculature. TNF-α–deficient mice show suppressed inflammation after MI, reduced cardiomyocyte death, and long-term cardiac dysfunction.[94] Direct administration[95] or forced adenoviral expression of soluble recombinant TNF-α receptor (TNFR)[96] inhibits TNF-α signals and reduced cardiomyocyte apoptosis and cardiac dysfunction,[97] supporting an early role for TNF-α in ischemic cardiac cell death. Cardiac reperfusion further stimulates TNF-α expression in

association with a depressed Bcl-2/Bax ratio, increased cytosolic caspase-8 and caspase-3 activity, and cardiomyocyte apoptosis.[98] In contrast, other investigators have reported that TNF-α could mediate cardiomyocyte survival. Gene therapy studies and overexpression of soluble TNFR blocked TNF-α signaling and promoted cardiac rupture in infarcted mouse hearts.[99] TNFR-1/TNFR-2 double-receptor knockout mice had a larger infarct and more cardiomyocyte apoptosis after MI.[100] TNFR-1 signals may be deleterious, mediating cardiac dysfunction, whereas TNFR-2 signals may be cardioprotective.[101] Thus, TNF-α appears to be a key regulator in ischemic cardiac death, with opposite biologic effects. Inhibition of IL-1 signaling with an IL-1 receptor antagonist (IL-1ra) blocks the effects of IL-1α and IL-1β, reduces caspase-9 activity, and protects cardiomyocytes from apoptosis after MI, but fails to modulate infarct size.[102] Viral delivery of the IL-1ra gene was successful in reperfused mouse hearts in reducing infarct size by 40% and apoptotic cardiomyocytes by 50%, and blocking the upregulation of Bax, Bak, and caspase-3,[103] suggesting an important role of IL-1 in the apoptosis that follows I/R.

TNF-α, IL-1β, TLR, the complement cascade, and ROS are all known to activate nuclear factor kappa B (NF-κB) in multiple cell types on cardiac injury.[104] This nodal transcription factor upregulates inducible chemokines and cytokines synthesis in infarcted hearts, and primes innate immune responses and exudative inflammation. However, NF-κB activation in leukocytes during the resolution phase of inflammation upregulates anti-inflammatory gene expression and apoptosis.[105] Transgenic mice deficient for p50, a key subunit of activated NF-κB, are partly protected against MI injury.[106] NF-κB can also upregulate inhibitor of apoptosis protein (IAP) and Bcl gene expression in certain cell types. Cardiac-restricted expression of a mutated IκB protein in transgenic mice prevented nuclear translocation of NF-κB, enhanced myocyte apoptosis, and increased infarct size after MI,[107] suggesting that NF-κB directly contributes to cardiomyocyte survival. NF-kB, like TNF-α, can trigger cytoprotective and apoptotic pathways and lead to contrasting findings in the heart. Both IL-1R and TNF-α pathways induce the long pentraxin PTX3 transcript in ischemic hearts[108,109] and in serum after I/R injury. PTX3-deficient mice show decreased capillary density and increased apoptotic cardiomyocytes after I/R, associated with increased complement cascade activation.[110] PTX3 may thus be a cardioprotective mediator of TNF-α and IL-1 signaling. Other soluble TNF-α family proteins, including TRAIL and CD40L, have been implicated in the development of MI. Enhanced expression of TRAIL was observed in circulating monocytes in MI patients, and human cardiomyocytes express the death domain–containing TRAIL receptor-1 and -2,[111] suggesting that the TRAIL system may participate in ischemic cardiac death. CD40L is also increased in the circulation of MI patients, but the relative contributions of TRAIL and CD40L in cardiac death after MI remain unclear. Cytokines of the IL-6 family, such as IL-6, cardiotrophin-1 (CT-1), and leukemia inhibitory factor (LIF) are induced after MI and have profound effects on cardiac myocytes by protecting them from apoptosis.[112] For example, CT-1, originally isolated as a promoter of hypertrophy, was subsequently found to reduce cardiomyocyte apoptosis in I/R injury in rats.[113] Experimental administration of CT-1 resulted in decreased infarct size, and forced expression of LIF prevented cardiomyocyte death and induced angiogenesis.[114] However, gene deletion of CT-1 or IL-6 does not modulate infarct size in mice after I/R injury, suggesting that alternative endogenous signals may compensate for their protective role.[115,116]

Hematopoietic Factors

Hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and monocyte colony-stimulating factor (M-CSF) are expressed in ischemic hearts.[117] The precise function of these growth factors is believed to promote inflammatory cell differentiation and function but remains mostly unknown. However, G-CSF can act directly on specific cardiomyocyte receptors to promote their survival.[118] G-CSF induced antiapoptotic Bcl-2 and Bcl-xL (B-cell lymphoma protein X, long isoform) expression and protected cardiomyocytes against ROS-induced apoptosis in vitro and I/R injury in mice. G-CSF also reduced apoptosis of endothelial cells and increased vascularization in infarcted hearts.[119] This is supported by the finding that treatment with G-CSF, stem cell factor (SCF), and other growth factors promotes mobilization of endogenous bone marrow progenitor cells, improves function, and attenuates left ventricular remodeling following MI.[120-123] M-CSF is stimulated in healing canine infarcts and its expression is associated with macrophage accumulation and proliferation. M-CSF does not directly reduce infarct area after MI, but stimulates vascular endothelial growth factor (VEGF) production, infarct vascularization, and reduced ultimate remodeling after I/R.[124]

CARDIAC DEATH AND TISSUE REPAIR

Anti-Inflammatory Cytokines

Acute inflammation is paired with formation of a reparative granulation tissue and progressive deposition of a collagen-rich extracellular matrix in the infarct area. This healing process is facilitated by the apoptosis of neutrophils that are cleared by other infiltrating inflammatory cells such as macrophages, production of anti-inflammatory cytokines, capillary growth, and stromal cell deposition.[125] TGF-β1 and IL-10, two powerful cytokines that antagonize the secretion of inflammatory cytokines, promote phagocytosis and mediate the transition to fibrosis via the activation of stromal cells.[6,126] TGF-β1 expressed in infarcted rodent hearts,[127] mainly in the infarct border zone,[128] plays the dual role of promoting transition from inflammation to fibrosis by downregulating the secretion of inflammatory cytokine and upregulating the synthesis of extracellular matrix, including collagen, fibronectin, tenascin, and proteoglycans.[129] TGF-β1 can attenuate MI injury when injected in the early stages of an infarcted heart.[130] Adenoviral overexpression of soluble TGF-β1 receptor type II inhibits TGF-β1 signaling and inflammatory cytokine production, and strikingly reduces interstitial fibrosis and ventricular remodeling in mice.[131] The anti-inflammatory effects of TGF-β1 are largely mediated by the signal transducers and transcriptional modulator Smad3, which are expressed in infarcted hearts.[132] Smad3-deficient mice have shown similar infarct size as their control littermates, but reduced remodeling and fibrosis.[133] Hence, increasing TGF-β1 may help reduce inflammation, whereas inhibition of TGF-β1 signaling via Smad3 may help reduce fibrosis and remodeling. In contrast with TGF-β1 manipulation, IL-10–deficient mice displayed no significant alteration in infarct size or cardiac function after I/R injury and no changes in cardiac remodeling. Moreover, treatment with recombinant IL-10 is not sufficient to limit ischemic inflammation,[134] indicating that multiple redundant pathways are present.

Granulation Tissue Formation and Apoptosis

Acute inflammation triggers angiogenesis in the infarct area, by myofibroblast proliferation and progressive deposition of a collagen-rich extracellular matrix, producing granulation tissue within 4 to 6 days. Tissue repair and angiogenesis in MI are controlled by numerous growth factors, including

VEGF, insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF)-AB, hepatocyte growth factor (HGF), and SCF. These growth factors are secreted in the lesions or released into the circulation.[5] They orchestrate tissue repair reactions within the infarcted area, mostly through the activation of supportive stromal cells, including fibroblasts and endothelial cells, as in other healing tissues. The angiogenic growth factors VEGF and bFGF are released within the first hours after infarction.[135] Despite important advances in our understanding of ischemic limb angiogenesis and cutaneous tissue repair, the healing mechanisms in infarcted myocardium are still little known. There is evidence that HIF-1α monitoring of hypoxia and early stimulation of VEGF secretion are critical for endothelial sprouting and angiogenesis.[136] Moreover, angiogenic angiopoietin-2 is increased, whereas its antiangiogenic counterpart, angiopoietin-1, is inhibited after MI in rats.[137] Endothelial cells are believed to originate primarily from resident vessels, with a few migrating from other organs to seed damaged hearts[138]; it remains possible that a small pool of endothelial cells originates from circulating progenitor cells.[139] Myocardial healing also involves tissue repair fibroblasts with phenotypic characteristics of smooth muscle cells (myofibroblasts), such as a contractile apparatus made of actin myofilaments and nonmuscle myosin.[140] These are the primary source of collagen in MI lesions, partly under the control of TGF-β1. Resident fibroblast proliferation has been amply documented[15]; some may also originate from circulating progenitor cells.[141] When active granulation tissue matures into a scar, apoptosis targets mainly interstitial cells, including endothelial cells, macrophages, and myofibrolasts.[35] Few infarct neovessels acquire a muscular layer to become permanent, whereas capillaries entirely devoid of mural cells regress.[142] PDGF-B signaling via its receptor PDGFR-β likely plays a critical role in recruiting mural cells to form neovessels.[143] Vascular regression may also result from proapoptotic TSP-1 accumulation in and around ischemic lesions.[43] Once dead, neutrophils are phagocytized and the remaining macrophages regulate collagen deposition by myofibroblasts[144] and contribute to extracellular matrix remodeling through the production of matrix metalloproteinases and their inhibitors. Supportive interstitial cells decrease markedly, further compromising cardiomyocyte survival, because the scar tissue is practically devoid of cellular components.[145,146] Hayakawa and colleagues,[147] using a murine model of administration of an antiapoptosis pan-caspase-inhibitor administered 4 days after the initial insult, imputed most of the deleterious effects of cardiac apoptosis to the death of granulation tissue cells and not to the ischemic cardiomyocytes. In this model, the inhibition of apoptosis prolonged myofibroblast survival and preserved capillary networks in the ischemic area, but failed to modulate cardiomyocyte death. Others have shown, however, that the subacute inhibition of apoptosis could reduce infarct area.

APOPTOTIC AND SURVIVAL SIGNALING IN MYOCARDIAL INFARCTION

Cardiac apoptosis is mediated by multiple highly regulated reactions involving proteases, kinases, and phosphatases (Fig. 9-2).

Intracellular Regulation of Apoptosis

On reception of an apoptotic signal, the response of each cell is influenced by the type of apoptotic trigger, the cell's ability to counteract this signal, and the expression and intracellular localization of several protein families that define the cell survival potential. In humans, intracellular modulators of apoptosis belong to two main signaling pathways, the extrinsic and intrinsic pathways.[32,148] Both are engaged by specific stimuli and culminate in the activation of cysteine–aspartic acid proteases (caspases), the terminal effectors for apoptosis. Briefly, the intrinsic pathway leads to the activation of procaspase-9 in response to a broad spectrum of stimuli generated when the mitochondrial integrity is compromised or a stress is imposed on the endoplasmic reticulum or nucleus. In the extrinsic pathway, procaspase-8 is activated and the apoptotic signals come from extracellular moieties binding cell surface receptors recruiting the so-called death domain adaptor proteins. All apoptotic signals are integrated at the mitochondrial level to be finely tuned by dedicated intracellular protein families, which include the Bcl, caspase, and IAP proteins.[149] However, novel apoptotic mediators not strictly operating through the classic pathways are being recognized regularly and the interest in defining transverse, or caspase-independent, apoptotic pathways is well maintained.

Death Receptor Activation

In the extrinsic pathway, apoptotic signals are transduced via specific cell surface receptors by cytokines such as TNF-α family proteins and other moieties in the cell microenvironment. The TNF-α/TNF-α receptor (TNFR), the TNF-related apoptosis-inducing ligand (TRAIL)/TRAIL receptor, the CD40/CD40 ligand (CD40L), and the Fas (CD95)/FasL systems are among the best understood.[32,148] On ligand binding, cell death receptors multimerize, inducing discrete conformational changes in their cytoplasmic tails and, more specifically, a gathering of their caspase-activation and recruitment domains (CARDs). This triggers the formation of the multimolecular death-inducing signaling complex (DISC). Briefly, multimerized receptors recruit death domain adaptor proteins such as TNFR-activated death domain protein (TRADD) for TNFR, and Fas-activated death domain protein (FADD) for Fas. In turn, the death domain proteins relocate the death effector domain (DED)-containing proteins, such as procaspase-8, to the cytoplasmic face of the plasma membrane. This spatial concentration of procaspase-8 enables a step of proteolytic autoactivation, generating a first burst of caspase-8 activity, also known as FADD-like IL-1β–converting enzyme (FLICE). The naturally occurring FLICE inhibitory protein (FLIP) inhibits caspase-8 activation and Fas-induced apoptosis.[150] FLIP expression determines the level of resistance of cardiomyocytes to Fas-induced apoptosis[89] and suppression of FLIP mRNA in cardiomyocytes sensitizes them to I/R apoptosis.[151]

Mitochondria

The pathways that link apoptotic signals to the mitochondria are unknown, but eventually they dysregulate the permeability and metabolic activity of the mitochondrial membrane.[149] MPT is characterized by the permeabilization of a relatively impermeable mitochondrial inner membrane leaflet in response to growth factor deprivation, hypoxia, I/R, oxidative stress, toxins, DNA damage, or radiation. MPT will cause the release of cytochrome C through the outer mitochondrial membrane leaflet into the cytosol, where it will trigger apoptotic programmed cell death. The extent of MPT appears to play a major role in I/R injury and myocardial infarction and eventually determines the fate of the cell. If minimal, the cell may recover from MPT; if severe, the cell may die from necrosis because of inadequate energy production.[1] Mitochondrial integrity and the metabolic activity essential for cell survival are guarded by the B-cell lymphoma (Bcl) protein family, Bcl-2, Bcl-xL and Mcl-1. Antiapoptotic Bcl proteins are inserted in the outer leaflet of the mitochondrial membrane

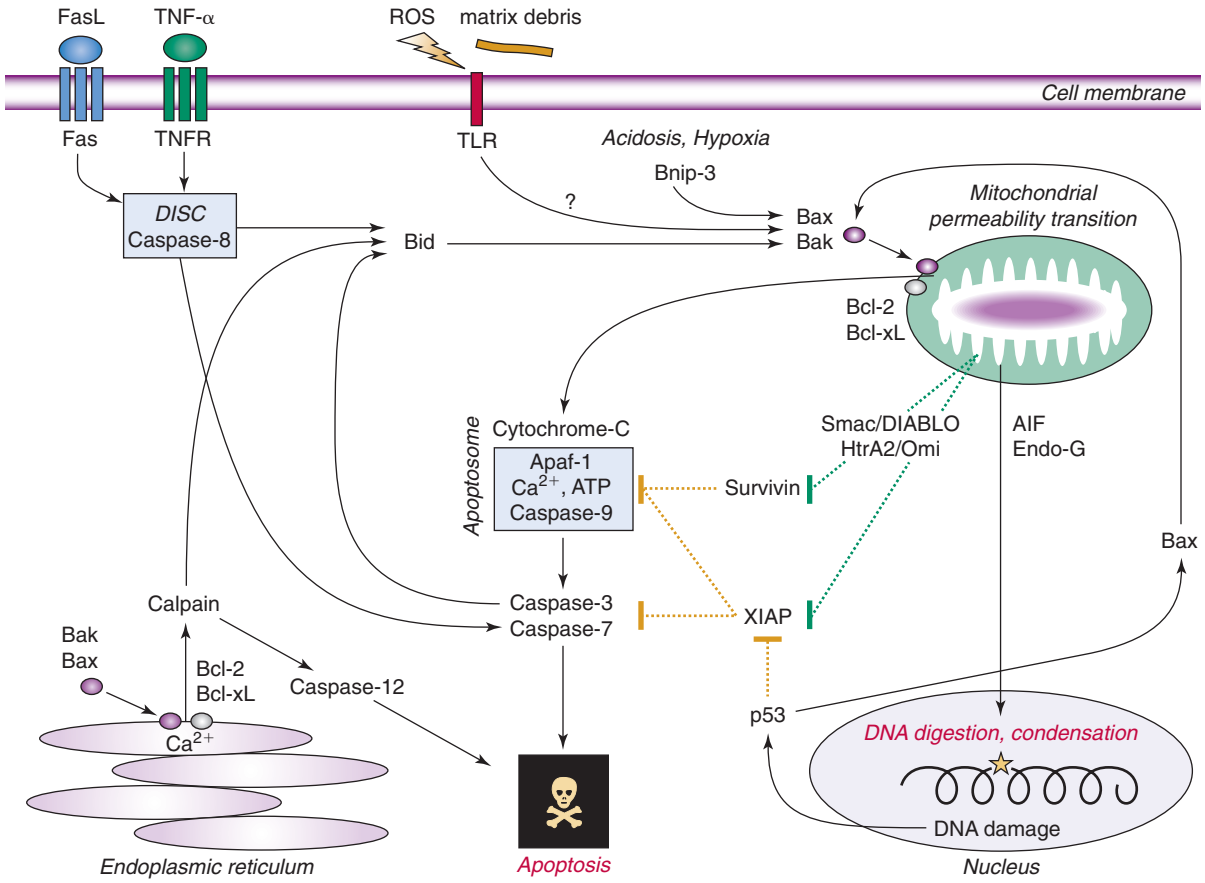

FIGURE 9–2 Apoptotic signaling in acute myocardial infarction. This figure summarizes some of the best-known apoptotic pathways engaged in MI. Apoptotic signals may be delivered via the extrinsic pathway through activation of death receptors such as Fas or TNFR by FasL or TNF-α. Multimerized death receptors trigger the formation of the intracellular multiprotein DISC, which promotes sequential activation of caspase-8 and effector caspases-3 and -7 that digest essential cellular components. The intrinsic pathway of apoptosis is an equally highly regulated process centred on the mitochondria and engaged by a greater variety of signals. Most apoptotic processes converge toward activation and translocation of proapoptotic Bcls, such as Bid, Bnip-3 Bax, and Bad. These factors counteract cytoprotective Bcl-2 and Bcl-xL, causing mitochondrial permeability transition pore opening and cytochrome C release. Cytochrome C forms the apoptosome in combination with APAF-1, ATP, Ca^{2+}, and procaspase-9. This triggers the sequential activation of caspase-9 and effector caspases. Bnip-3 is activated by acidosis and hypoxia, whereas cytoplasmic Ca^{2+} elevation sparks up calpain activity, caspase-12 activation, and truncation of Bid. ROS can damage DNA, causing Bax expression under the control of p53 and mitochondrial permeability transition. ROS can also activate TLRs, which will modulate gene expression and induce or inhibit apoptosis, depending on cell type. Bax and Bak appear to play a similar function in the endoplasmic reticulum, controlling Ca^{2+}release. Caspase-activity can be inhibited by survivin or XIAP, which can be antagonized by their own inhibitors, smac/DIABLO and HtrA2/Omi. The release of mitochondrial AIF and endonuclease-G (Endo-G) triggers caspase-independent DNA condensation.

and prevent the release of mitochondrial proteins. Other multidomain Bcl proteins, such as Bax and Bak,[152] are multidomain proapoptotic proteins. Bax is sequestered in the cytosol when inactive, but apoptotic signals cause its dephosphorylation and relocalization to the mitochondrial membrane, where it forms ion- and water-permeable pores that trigger mitochondrial depolarization and MPT pore opening.[153] Either Bax or Bak is necessary to intrinsic initiation of apoptosis, because cells lacking both proteins are resistant to this pathway.[154] A third Bcl subgroup formed by BH3-only proteins, including Bad, Bid, Bim, and BCL2/adenovirus E1B 19-kDa protein-interacting protein-3 (BNIP-3), can monitor specific intracellular signals and transmit proapoptotic information to Bax or Bak. One hypothesis is that Bcl-2 and Bcl-xL interact with the translocated Bax or Bak to mediate MPT; another is that they function as a sink for BH3-only proteins to prevent activation of Bax and Bak.[155] In turn, MPT will cause mitochondrial swelling and cytochrome C leakage into the cytosol, as well as external membrane rupture. Cytochrome C binds apoptosis protease-activating factor-1 (APAF-1) and procaspase-9 in the cytosol to make up the apoptosome in the presence of Ca^{2+} ions and dATP.[156] Caspase-9 recruitment by the apoptosome and autoactivation feeds into the final caspase-pathway. Hence, the balance between proapoptotic and antiapoptotic Bcl proteins determines MPT and cell fate.

One week after cardiac infarction in humans, cell death is associated with a significant upregulation of proapoptotic Bax expression.[88] The contribution of Bcl proteins to I/R injury has been established in transgenic mice, revealing over 50% reduction in infarct size in Bax-deficient mice.[157] In many cell types, apoptosis is dependent on p53 transcription factor signaling and induction of Bax expression.

Novel regulators of Bcl protein activity and MPT pore opening that have recently been described include the apoptosis repressor with caspase-recruitment domain (ARC), known to interact with Bax and inhibit cytochrome C release. ARC is downregulated by cardiomyocyte exposure to hypoxia or oxidative stress and correlates with cell death in vitro.[158] BNIP-3 is an atypical BH3-only Bcl protein that is induced

by acidosis and hypoxia. On activation by ischemia or acidosis, BNIP-3 interacts with Bcl-2 or Bcl-xL to induce apoptosis and DNA condensation, partially independent of caspase-activation and cytochrome C release.

Mitochondrial Signaling and Autophagy

Autophagy is thought to provide a further regulatory step for apoptosis. Indeed, BNIP-3 transfection in vitro stimulates autophagosome assembly and necrosis, providing a signal interconnecting apoptosis, necrosis, and autophagy.[159] Pro-autophagic beclin-1 overexpression downregulates Bax activation and protects cardiomyocytes from I/R injury.[11] Beclin-1 is also expressed during deleterious heart reperfusion and is associated with cardiomyocyte death.[12] Further work is necessary to determine the nature of MPT, Bax, and other Bcl protein crosstalk with autophagy pathways and whether they play a protective or deleterious role during cardiac ischemia.

Caspase-Activity

Caspases are activated downstream of the extrinsic and intrinsic pathways. Caspases-8 and -9 activate the terminal caspases-3 and -7, which execute cell fragmentation through the digestion of key intracellular target proteins (e.g., cytoskeleton, kinases), activation of Ca^{2+}-dependent endonucleases, internucleosomal cleavage and chromatin condensation, and ultimate disruption of the cell. Specific proteolytic site inhibitors of caspases, such as the tripeptide multicaspase-inhibitor Z-Val-Ala-Asp(OMe)-CH2F (ZVAD-fmk), reduce MI injury by 20% to 40%[160] and block the uptake of radiolabeled annexin V in mice after MI.[161] It was also reported that activity of caspases-3 and -8 was significantly greater in I/R injury versus ischemia alone.[98] Caspase-activity inhibitors reduce myocardial infarct size by 20% to 30% after I/R injury, lower the proportion of apoptotic cardiomyocytes by 70%,[162,163] and improve cardiac function,[164] illustrating the impact of cardiac apoptosis.

Endoplasmic Reticulum Stress

As a major reservoir of intracellular Ca^{2+}, the endoplasmic reticulum (ER) has been shown as a potential apoptosis initiator through the release of Ca^{2+} into the cytoplasm. Bcl-2 and Bcl-xL are both found at the cytoplasmic face of ER membranes.[149] Bax and Bak expression are known to increase ER Ca^{2+} stores, thereby facilitating Ca^{2+} spikes and apoptosis,[152,165] whereas Bcl-2 has opposite effects.[166,167] On stimulation, ER-released Ca^{2+} may participate in the activation of Ca^{2+}-dependent proteinases, including calpain, which in turn will activate caspase-12[168,169] and cleave essential elements of the cytoskeleton and Bid[170] to induce MPT and apoptosis.

Endogenous Caspase-Inhibitors: Inhibitors of Apoptosis

When caspases are activated, cells can escape death through endogenous caspase-antagonists. Proteins grouped in the IAP family, such as X-linked inhibitor of apoptosis protein (XIAP) and cellular IAP-1 (cIAP-1) and -2, can block the catalytic site of caspases and the proteolytic steps necessary to apoptosis.[171] Others, such as survivin, can inhibit apoptosome activity[172] and mitochondrial damage.[173] It was found that XIAP is degraded after MI in mice[174] and XIAP expression is depressed after 1 week in human cardiac infarcts, concomitant with significant apoptotic cell death and caspase-8 activation.[88] Cardiomyocytes are remarkably resistant to cytosolic microinjection of cytochrome C compared with other cells, probably because of their low expression of its cytosolic partner, APAF-1. However, XIAP-deficient cardiomyocytes die rapidly in response to cytosolic cytochrome C.[175] IAP survivin inhibits apoptosis and regulates cell division in vascular[176] and cancer cells.[177] Survivin is not found in resting healthy human hearts but is induced in peri-infarct cardiomyocytes after MI, and it is inversely correlated with cardiomyocyte apoptosis and cardiopathy.[178] A somewhat contrasting study has reported recently that survivin is induced in human cardiomyopathy, but downregulated after hemodynamic support by a left ventricular assist device.[179] In vitro, small interfering RNA knockdown of survivin in neonatal rat cardiomyocytes leads to polyploidization and cell cycle arrest, whereas forced adenoviral expression inhibits apoptosis and promotes DNA synthesis and cell cycle progression.

MANAGING CELL DEATH IN MYOCARDIAL INFARCTION

Spontaneous cardiac regeneration is negligible after serious injury. Understanding and manipulating myocardial survival in patients appears particularly desirable to compensate for the irreversible cell loss and ultimately preserve the global integrity of the heart—that is, smaller infarcts and less remodeling strain on intact myocardium. A number of different approaches have been used and are being developed to trigger timely expression of cytoprotective gene programs and optimize the survival of cardiomyocytes and cardiac vascular and progenitor cells.

Preconditioning

Hearts exposed to short episodes of ischemia develop a relatively higher resistance to MI and I/R injury, a phenomenon termed *ischemic preconditioning* (IPC). IPC is the most powerful endogenous cardioprotective mechanism known (see Chapter 24 for details). Understanding its cellular and molecular bases may lead to novel therapeutic approaches to prevent ischemia and reduce its complications. Typically, ischemic preconditioning is achieved by applying one or several short-term cycles (5 to 30 minutes) of I/R prior to a more prolonged interruption of coronary flow and final reperfusion. IPC affords protection against oncosis and apoptosis. It directly inhibits caspase-3[180] and attenuates radiolabeled annexin V incorporation,[161] apoptotic cell death, and infarct size.[181] IPC can preserve left ventricular functional reserve and increase coronary blood flow and capillary perfusion.

Cardiac protection achieved with IPC is potent, but confined to specific conditions and time windows. Early or immediate IPC persists for 4 hours after the occlusion, whereas delayed or late IPC lasts for up to 72 hours. Late IPC involves gene regulation and protein synthesis; early IPC does not. Superoxide radical scavengers and hydroxyl radical scavengers inhibit the benefits of IPC in infarcted myocardium, suggesting a crucial role for ROS signaling, more so for late cardioprotection and angiogenesis.[182] IPC is mediated by the activation of transcription factors such as hypoxia-inducible factor-1α (HIF-1α),[183] NF-κB, transcription factor-IID, signal transducer and activator of transcription (STAT) 3, and SP1.[136] IPC activation of NF-κB is associated with delayed cardioprotection via NOS upregulation and increased NO production, and the elective inhibition of NF-κB increases the benefits of IPC.[184] Whether these effects are mediated predominantly through NOS2[185] or NOS3 activity is unclear.[186] β-Catenin is also involved in IPC cardioprotection and induction of Bcl-xL,[187] Bcl-2, and survivin expression in rat hearts.[188,189] IPC is also associated with reduced apoptosis-inducing factor (AIF) mitochondrial-nuclear translocation on reperfusion.[190] In addition, IPC upregulates the expression of

endothelial cytoprotective and angiogenic growth factors such as VEGF. Hence, the cardioprotective effects of IPC may stem from the expression of endogenous blockers of MPT pore opening and anticaspase-inhibitors in cardiomyocytes, as well as increased angiogenesis.

The cardioprotective effects of IPC can be mimicked in many ways. Thermal preconditioning with temperatures up to 42° C acts by inducing heat shock transcription factor-1 expression[180] and increasing heat shock protein (HSP)-70 and HSP-90 expression. Preconditioning with opioids and volatile anesthetics, including isoflurane derivatives, induces cardioprotection in relation to ROS[191] and NF-κB activation.[192]

Postconditioning

In ischemic postconditioning, the timing of ischemic periods is made once infarction has occurred. It is effective when applied within minutes of reperfusion[193,217] to reduce radiolabeled annexin V uptake,[161] suggesting a reduction of apoptosis. It also reduces the expression and activity of JNK (c-Jun-NH2 terminal kinase) and p38-MAPK (mitogen-activated kinase), the expression of Bax and TNF-α, and apoptosis.[98] Ischemic postconditioning operates through the inhibition of endoplasmic reticulum stress[194] and increased cardiac Bcl-2 expression. It is mediated in part by p38-MAPK-mediated upregulation of calreticulin.[195] Hence, p38-MAPK activation, which appears detrimental after infarction, may in fact help promote protective ischemic postconditioning.

REGENERATIVE CELL THERAPY

Cell therapy is seen as a promising possible approach to protect and reconstitute cardiac tissue, with the ambitious goal of restoring contractile cells and replacing dead cardiomyocytes after MI.[121] Skeletal myoblasts were first administered to patients with subacute MI. For reasons that are not entirely clear, these cells failed to regenerate or improve cardiac function, and were arrhythmogenic.[196,197]

Progenitor cells attract attention for their availability and potential to differentiate and acquire a contractile and electrophysiologic phenotype. Progenitor cells from placental cord blood and adult tissues, including bone marrow mesenchyma, adipose tissue and myocardium, have shown potential for cardiac muscle differentiation. Results were mitigated, however, and many studies in rodents or patients after MI concluded that bone marrow–derived cells and circulating blood-derived progenitor cells were no better than skeletal myoblasts.[198,199] More promising results were reported recently in animal models with the coadministration of myoblasts and hematopoietic stem cells in border zones and scars of 4-week-old infarcts.[200] It was hypothesized that hematopoietic progenitors could enhance myoblast survival by secreting survival factors. Another possible mechanism could be a reduction in apoptotic and oncotic reactions of surviving cardiomyocytes.

Progenitor cells were also considered for their potential to reconstitute a vascular bed in infarcted areas. Hematopoietic stem cells exhibit bipotential hemangioblast activity during adult life. Adult endothelial progenitor cells (EPCs) originating from the bone marrow and potentially related to HSC or hemangioblasts can mobilize, migrate to the general circulation, and home to sites of active vessel growth, a process termed *adult vasculogenesis*.[201-203] Angiogenic EPCs have been identified in bone marrow mesenchymal stem cells and in other tissues, including adult adipose tissue and placental cord blood–derived stem cells. Several clinical trials have been conducted that administered unfractionated versus sorted human bone marrow cells into ischemic hearts (REPAIR-AMI, BOOST, ASTAMI, Janssen trials). The results of these trials are still a matter of discussion. In general, they have shown no striking clinical benefits; nevertheless, an improvement in ejection fraction following the intracoronary administration of bone marrow–derived progenitor cells has been reported.[204-206] These benefits were more evident in patients with more severe infacts,[205] but other trials failed to reproduce such improvements.[207,208] These discrepancies have been imputed to various factors, including cell-sorting methods, duration of the isolation procedures, storage conditions, timing and route of administration, patient characteristics, and other technical issues. Of interest, it was also shown that the presence of cardiovascular disease or risk factors such as diabetes, obesity, smoking, or dyslipidemia could compromise the survival and function of progenitor cells in their niche of origin (bone marrow, fat tissue) and also in target tissues. Whether progenitor cells influence resistance to ischemic apoptosis or possess significant therapeutic value clinically remains to be documented with more definitive data.

Timing of Administration

With current reperfusion therapy, one would expect that early cell infusion would be more effective to preserve heart function. Revascularization via cell therapy, however, differs from mechanical recanalization in that transplanted cells are sensitive to the proapoptotic microenvironment. The timing for administration should therefore be carefully synchronized to avoid hostile apoptotic activity, because progenitor cells may disappear, along with dying neutrophils, endothelial cells, and supporting stromal fibroblasts. The enhancement in the formation of granulation tissue by cell therapy may also overtax the removal of the apoptotic fragments that need to be cleared during the phase of tissue remodeling. Progenitor cell administration during the acute inflammatory phase was of no benefit in most trials.[207,208]

Progenitor cells also might not be able to survive when administered of acellular postinfarct scars, when capillaries have rarefied. Similarly, the administration of skeletal myoblasts 10 to 14 days post-MI failed to produce benefits and even worsened the clinical outcome.[196,197] Much work remains to be done to determine the optimal timing for cell delivery during the complex and overlapping processes of ischemia, inflammatory, oncosis, apoptosis, and healing in MI (Fig. 9-3).

Transplanted Progenitor Versus Endogenous Cell Survival

The death of endogenous cardiac cells needs to be distinguished from that of transplanted progenitor cells. Some reports have suggested that an antiapoptotic treatment could enhance the survival of progenitor cells and be beneficial in MI. Forced expression of antiapoptotic Bcl-2 can confer increased resistance to apoptosis of rat mesenchymal stem cells, stimulate VEGF secretion, and enhance the protective effects in cell therapy.[209] More recently, it was suggested that hypoxic preconditioning of bone marrow mesenchymal stem cells before their transplantation in infarcted hearts could stimulate expression of HIF-1 and antiapoptotic genes, such as Bcl-2 and Bcl-xL. Hypoxic preconditioning of progenitor cells also enhances proangiogenic growth factor expression, including angiopoietin-1, erythropoietin, VEGF, and its receptor, Flk-1, and extends their own survival in vitro and in vivo.[210,211]

EPCs release a panel of paracrine growth factors and cytokines that possess cytoprotective effects on vascular and cardiac cells, including VEGF,[165] IGF-1, EGF, and PDGF, an

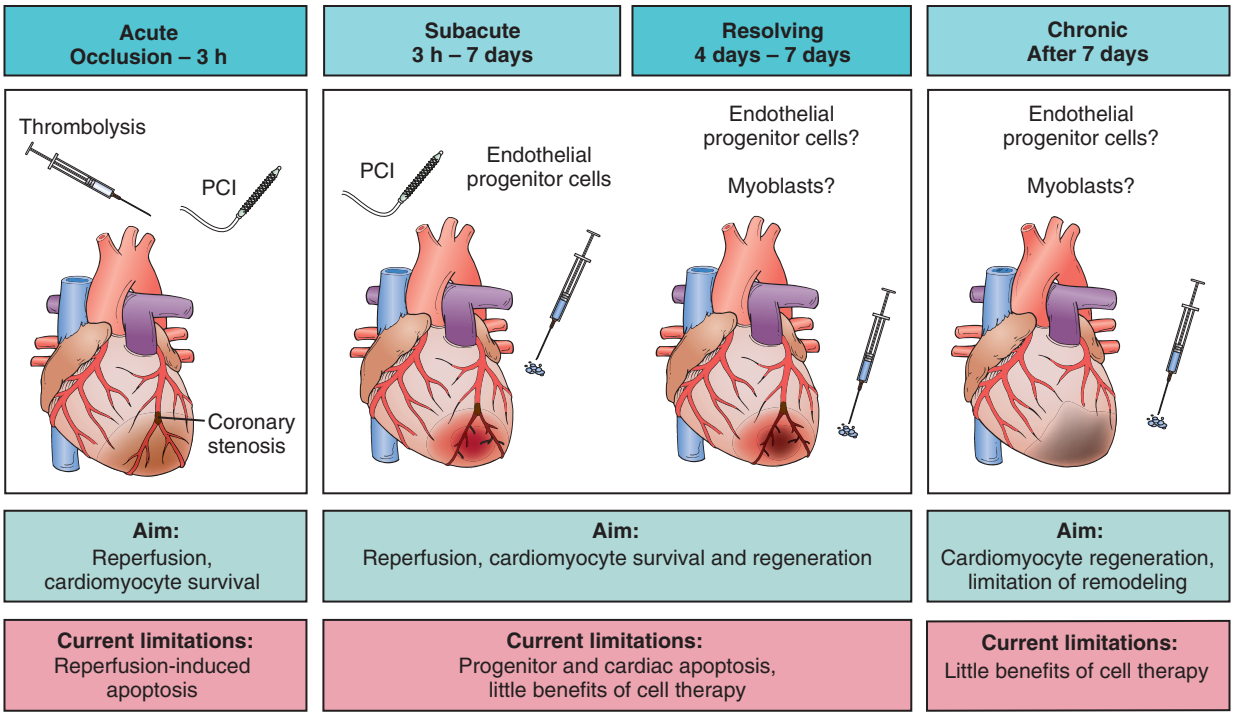

FIGURE 9–3 Potential schedule of cell therapy after acute myocardial infarction. Current primary care for acute myocardial infarction involves the rapid revascularization of culprit-stenosed coronary arteries via thrombolytic agents or transluminal percutaneous angioplasty. The sooner the reperfusion, the better the chance of survival. Maximal benefits are obtained within the first 3 hours after occlusion, when acute inflammation develops. However, sudden reperfusion causes further cardiomyocyte death at this time. When possible, delayed percutaneous coronary intervention (PCI) may be deployed sucessfully for several days after limited stenosis, especially when there is a threat of MI extension. Alternative and complementary therapy have been designed, with debated success, including progenitor cell administration. Endothelial progenitor cells may help revascularize infarcted areas and promote cardiomyocyte survival. Skeletal myoblasts or cardiac progenitor cells may contribute to cardiomyocyte regeneration. However, timing of administration is critical. Progenitor cells delivered before or during the resolution of inflammatory and tissue repair reactions may die without producing benefits. Conversely, progenitor cells inserted in scar tissue may not be able to survive or increase contractility. Further work is needed to regulate cell death and regeneration in acute MI successfully.

effect particularly marked under hypoxic conditions.[212-215] Cell therapy using rat myoblasts expressing VEGF improved heart function recovery and lowered cardiomyocyte death in a model of I/R injury.[216] Transplantation of cells engineered to overexpress stromal cell–derived factor-1 (SDF-1) into the border zone significantly reduced remodeling in rats[217] by a mechanism that promoted stem cell homing into the treated lesions, enhancing neovascularization and cardiomyocyte survival.[218] These observations support the concept that the secretion products of transplanted progenitor cells enhance the survival of cardiomyocytes and endothelial and other granulation tissue cells. Although most transplanted human EPCs had disappeared within 1 week in a study of immunodeficient ischemic mouse myocardium, the cytoprotective and angiogenic growth factors such as VEGF, HGF, IGF-1, and SDF-1 remained highly expressed and secreted by the ischemic host tissue for an unexpectedly long time.[219] This was associated with a threefold decrease in cardiomyocyte apoptosis and a 10-fold increase in cell proliferation. Another study has shown that transplantation of allogenic mesenchymal stem cells after MI promotes cardiomyocyte proliferation and reduces apoptosis independently of myocardial differentiation and cardiomyocyte proliferation,[220] suggesting that transplanted progenitor cells can increase survival and proliferation of endogenous progenitor cells. This is further supported by the finding that treatment with SCF, G-CSF, and other growth factors can promote mobilization of endogenous bone marrow progenitor cells, improve myocardial function, and attenuate left ventricular remodeling following MI.[120-122] A clinical correlate is found in the observation that bone marrow progenitor cell administration can prevent long-term remodeling.[208] Hence, certain progenitor cells may promote the survival of endogenous cardiomyocytes through the postischemic inflammatory and tissue remodeling phases. The underlying hypothesis is that progenitor cells release secretions that prime specific tissue repair reactions which persist beyond their death. This response to cell therapy will be influenced by the ability of the host tissue to secrete the appropriate growth factors and cytokines when progenitor cells are present. In this regard, interventions that could prolong the survival of progenitor cell survival could be a very positive asset.

Progenitor Cell Microenvironment

The microenvironment in which progenitor cells home and anchor is critical to their survival and function. This environment can be nonfriendly, such as a host tissue that compromises resident vascular tissues and cells or a site of intense proapoptotic activity or a toxic stimulus. No animal models of I/R can reproduce the complex pathophysiologic mechanisms implicating dysregulated inflammatory cytokines, autoimmune activity, or complement activity, to mention but a few. Expecting that EPCs will be resistant to apoptosis and highly proliferative in such settings may thus be inappropriate. The relative resistance of regenerative cells, whether progenitor or mature vascular cells, to the apoptotic stimuli induced by oxidized low-density lipoproteins, TNF-α, or other active compounds remains largely unknown. Moreover, we have recently been able to show that the levels of humoral

factors in the cell transplantation recipient, such as adiponectin, condition the success of proangiogenic cell therapy.[221] Furthermore, many drugs, including cyclo-oxygenase (COX)-2 and -1 inhibitors, antiaggregants, antithrombins, statins, and opioids can affect the infarcted heart microenvironment. Bone marrow–derived endothelial progenitor cells express both COX-1 and COX-2 in vitro. Anti–COX-2 agents such as celecoxib can reduce Akt (protein kinase A) phosphorylation in EPCs, trigger PS externalization, and initiate caspase-3 activation.[222] EPCs may thus become targets for classic COX-2 inhibitors and prevented from participating in vasculogenesis. In addition, progenitor cells adhere to activated platelets and respond to platelet-released stromal cell–derived factor-1 alpha (SDF-1α), suggesting that platelets could anchor circulating EPCs to ischemic tissues and provide paracrine stimulation for proper homing.[223,224] Common antiplatelet treatment and aggregation inhibitors such as GP2b3a and P2Y12 inhibitors are thus expected to interfere with optimal EPC function. Thus, some of the first-line medication administered to acute coronary syndrome (ACS) and MI patients may not be successfully combined with cell therapy, as currently envisioned by some researchers. On the other hand, statins exert pleiotropic effects via multiple anti-inflammatory and vasculoprotective signaling cascades[225]; in EPCs, they stimulate Akt activity, decrease Bim expression and increase resistance to ROS- and TNF-α–induced apoptosis.[212,226]

STUDIES ON CELL REGENERATION AND APOPTOSIS IN MYOCARDIAL INFARCTION

A number of studies are now investigating novel issues relative to cell death and byproducts, as discussed in this section.

Dead Cell Clearance

The rate of apoptotic cell clearance may be as important as the rate of cell death to maintain tissue homeostasis. *Lactadherin*[227] or *c-Mer kinase* genes[228] are two key elements in apoptotic cell phagocytosis; the inactivation of one of these genes prevents the recognition of apoptotic cells by phagocytes, which results in the accumulation of cell debris and growth of the atherosclerotic plaque while favoring the dispersal of "self" antigens in damaged tissues and autoimmune inflammation.[229] Conversely, the removal of apoptotic cells leads to the release of powerful anti-inflammatory cytokines such as IL-10[126] and TGF-β1,[6] which contribute to the resolution of inflammation. Thus, the lesson derived from the study of atherogenesis may apply to infarcted hearts, and cell death should be coupled with efficient and timely removal of debris to prevent excess secondary inflammation. How much apoptotic cell clearance pathways contribute to MI injury is still unknown, but modulating the rates of phagocytosis could be expected to affect infarct size and subsequent remodeling.

Cell Death and Byproducts

Dead cell fragments and particles produced by the fragmentation of apoptotic cells may not be devoid of physiologic functions, but they carry signals capable of modulating inflammation and tissue homeostasis. A class of dead cell fragments named microparticles (0.2 to 1 μm in diameter) derived from apoptotic endothelial cells or from EPCs are capable of stimulating endothelial proliferation, resistance to apoptosis, and pseudocapillary tube formation. Apoptosis byproducts may thus raise the vasculogenic potential of progenitor cells and participate in the repair process under certain circumstances. Endothelial microparticles, in particular, contain active messenger RNA and lateral transfer of biologic information may modulate vascular cell fate, including survival and differentiation.[230] This adds complexity to the picture of cell survival and death pathways in MI. Similar microparticles can also originate from activated cells.

Secondary Effects of Progenitor Cell Therapy

Despite careful selection and evaluation of progenitor cells for transplantation cell therapy, introduction of progenitor cells may exert a number of putative negative effects that have barely been characterized. Aside from the risks of iatrogenic oncogenesis, which was not reported with progenitor cells in the heart, the administration of undifferentiated cells with high proliferation potential may modify distal pathologic processes. More specifically, bone marrow progenitor cells can penetrate atherosclerotic lesions and promote their growth in situations of ischemia.[231] Hence, bulk delivery of progenitor cells could favor the progression of atherosclerosis in the vasculature of diseased hearts or remote lesions. The artificial introduction of therapeutic cells in diseased tissues can contribute to apoptosis and local accumulation of cell fragments. This underestimated aspect might influence the outcome of cell therapy.

CONCLUSIONS

Cardiac cell death and regeneration have been extensively studied in ischemic and reperfused hearts over the past decades. These studies have revealed that ischemia and reperfusion trigger highly regulated signaling pathways, resulting in cell demise, and that spontaneous cardiac regeneration is poor. Numerous molecular and cellular modulators of cell death and regeneration have been identified in the heart. Blocking a single mediator of cell death in MI results, in the vast majority of animal studies, in no more than a 50% reduction in infarct size. This suggests that multiple cell death pathways are engaged and cross-regulated in infarcted hearts. It is remarkable that despite the numerous positive animal studies, no specific antiapoptotic drug or regenerative therapy could successfully reduce infarct size in humans. Although species differences may account for some of these failures, a more comprehensive perspective suggests that ischemia and reperfusion in humans may respond to more sophisticated molecular and cellular pathways. Successful modulation of cardiac cell death may thus require finer tuning than direct blockade of a single pathway. Novel therapeutic designs will require an exquisitely refined understanding of the compartmentalization of cell death. Innovative pharmacologic and drug delivery methods targeting specific cell populations may help make the most of our current knowledge of cardiac cell death. Further development in cell therapy, coupled with the manipulation of survival pathways, may partly fulfill the ultimate dream of cardiac regeneration.

Acknowledgments

This work was supported by a grant from the Agence Nationale pour la Recherche ANR-07-PHYSIO-025-01 awarded to Dr. Olivier Blanc-Brude. The Centre National pour la Recherche Scientifique (CNRS) provided salaries and the Institut National pour la Santé et la Recherche Médicale (INSERM) contributed general support.

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CHAPTER 10

Pharmacogenomics

Simon de Denus, Catherine Labbé, Michael S. Phillips, Jean-Claude Tardif, and John D. Rioux

Cardiovascular disease (CVD) remains the leading cause of mortality in the world, with more than 15 million deaths each year. With the current rise in obesity and other cardiovascular risk factors in the general population, it is anticipated that we will see a further increase in the incidence of heart disease in the coming decades, leading to an increase in CVD-related mortality and morbidity and an increased burden on the health care system.

The pharmacologic treatment of acute coronary syndrome (ACS) and the secondary prevention of coronary artery disease (CAD) have grown more complex as the result of many clinical trials demonstrating reductions in major cardiovascular events with the use of multiple classes of medications, including antiplatelet agents (e.g., aspirin, clopidogrel, glycoprotein IIb/IIIa [GPIIb/IIIa] inhibitors), fibrinolytics (e.g., streptokinase, alteplase), anticoagulants (e.g., heparin, low-molecular-weight heparins, fondaparinux), as well as statins and neurohormonal inhibitors (e.g., beta blockers and angiotensin-converting enzyme inhibitors [ACEIs]). In addition, many patients have several risk factors (including dyslipidemia, hypertension, and diabetes) that are treated with a number of medications, raising safety issues related to drug interactions and adverse drug reactions (ADRs). However, although the efficacy and safety of these drugs in specific populations have been demonstrated, there are currently only limited data available for the health professionals to identify specific patients who benefit from these drugs (responders), those who require alternative dosing strategies, or those who are at greater risk of experiencing ADRs.

ADRs represent a leading cause of mortality, morbidity, and cost.[1,2] Mounting evidence has demonstrated that bleeding secondary to the treatment of ACS with antiplatelet agents, anticoagulants, or fibrinolytics adversely affects the prognosis of patients.[3] Hence, the identification of predictors of this ADR has become an important focus of research. Moreover, there is no known marker that can reliably identify patients most likely to experience rare, yet devastating, idiosyncrasic ADRs from many of the drugs used in the treatment and secondary prevention of ACS (e.g., heparin-induced thrombocytopenia, ACEI-induced angioedema, statin-induced myotoxicity). Thus, although significant progress has been made in the treatment of CVD, clinicians and drug policy makers recognize the importance of developing effective strategies to address drug efficacy problems and reduce ADRs resulting from CVD treatment.

Age, gender, ethnicity, weight, and renal and hepatic function are known modulators of drug pharmacokinetics—what the body does to the drug (the relationship between medication dose and plasma concentration) and pharmacodynamics—what the drug does to the body (the relationship between plasma concentration and medication effect). Nonetheless, they explain only a limited fraction of intersubject variability of drug response.[4] Genetic factors may also contribute to this intersubject variability. Some have estimated that 20% to 95% of this variability may be attributable to genetic factors.[5] Given the extensive data supporting the impact of genetic variations on the metabolism of many drugs used in the treatment and secondary prevention of ACS and the heritability of many drug targets,[6-10] genetic factors may significantly contribute to the intersubject variability observed in the response to ACS pharmacotherapy. The field of pharmacogenomics aims to discover these genetic determinants to identify individuals who are most likely to respond, experience an ADR, or benefit from an alternative dosing regimen for a given drug.[11] Understanding the genes that influence cardiovascular drug efficacy and toxicity may eventually provide guidance to health professionals for the optimization of pharmacotherapy for ACS and other CVDs.

Unfortunately, pharmacogenomic data are limited in ACS. Moreover, given the fact that no genetic test is currently used in clinical practice for the treatment of CVD, the objective of this chapter will be to illustrate the complexity of genomics and pharmacogenomics and how they can potentially influence the treatment of ACS and the secondary prevention of CAD. Following is a glossary of terms used in this chapter.

Glossary

Adverse drug reaction An unwanted effect caused by the administration of a drug. The onset of the adverse reaction may be sudden or may develop over time.

Allele In association studies, the term *allele* is most commonly used when referring to markers. An allele would be one specific version of a marker inherited from a parent (e.g., A or T in the case of an A/T SNP). Allele is also used in a broader context when referring to a specific version of an entire gene.

Association testing and association-based approaches A genetic variant is genotyped in a population for which phenotypic information is available (such as disease occurrence or a range of different trait values). If a correlation is observed between genotype and phenotype, there is said to be an association between the genetic variant and the disease or trait.

Causal gene The specific gene responsible for the risk conferred by a genomic region identified by an association study.

Causal variant The specific DNA sequence that functionally gives rise to the increased risk conferred by a genomic region identified by an association study.

Genetic markers Genomic variants used as positional tools to associate specific DNA fragments to certain phenotype or disease.

Genome-wide linkage scan A linkage study performed with markers located across the entire genome. It is traditionally performed with approximately 300 markers of simple sequence length repeats (SSLPs) and, more recently, with approximately 5000 SNPs.

Genotyping A test designed to identify the genetic constitution of an individual—that is, the alleles present at one or more specific loci.

Haplotype A haplotype is a combination or pattern of alleles at multiple linked loci that are transmitted together.

HapMap Genetic resource created by the International HapMap Project (www.hapmap.org). The HapMap is a catalogue of common human genetic variants that occur. It describes these variants, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world.

Linkage disequilibrium (LD) A situation in which alleles on the same chromosome occur together more often than can be accounted for by chance. This indicates that the alleles are physically close on the DNA strand and are most likely to be transmitted together within a population.

Linkage study A study aimed at establishing linkage between a genetic marker and a disease locus. Linkage is based on the tendency for genes and genetic markers to be inherited together because of their location near one another on the same chromosome.

Locus The specific position of a gene or a marker on a chromosome.

Penetrance The likelihood, under given environmental conditions, with which a specific phenotype is expressed by those individuals with a specific genotype. For example, if half (50%) of those with the gene "X" that is known to cause the disease actually have the disease, then the penetrance of the gene is 0.5.

Pharmacodynamics Refers to the study of effects produced by drugs through interactions with their targets (receptors, enzymes, others), their mechanism of action, and the relationship between drug concentrations and effects (what the drug does to the body).

Pharmacokinetics Refers to the study of the time course of a drug and its concentration during its absorption, distribution, metabolism, and excretion in the body (what the body does to a drug).

Poor metabolizer A person who metabolizes a drug at a slower rate than others. A person can be a poor metabolizer for one drug and an extensive metabolizer of another, depending on the enzymes implicated in the metabolism of the drugs and the genotypes of the patient for these enzymes.

Replication study A study designed to test (or replicate) a prior, and explicit, genetic hypothesis.

Single nucleotide polymorphism (SNP) A genomic variant in which a single base in the DNA differs from the usual base at that position.

Tag SNP A representative SNP in a region of the genome with high linkage disequilibrium. This allows genetic variation to be identified without genotyping every single SNP. Tag SNPs are significant in genome-wide association studies in which millions of SNPs across the genome are studied. Tag SNPs allow the number of SNPs to genotype to be reduced while generating the same amount of information. The HapMap Project has catalogued tag SNPs in the entire human genome.

STRUCTURE OF THE HUMAN GENOME

The human genome consists of 3.3 billion base pairs of DNA. The recent completion of the human genome sequence provides evidence for 20,000 to 30,000 genes encoded by the genome of every individual nucleated cell of the human body.[12] The genomic code, consisting of four different nucleotides (most often referred to by their single-letter symbols—A, C, G, T), has long been established. More recent studies have demonstrated that there are numerous differences that can be identified when comparing the genome of any two individuals. These are known as genetic variants. Although there are many different forms of genetic variation (e.g., insertions and deletions, rearrangements), the most common form is that of the single nucleotide polymorphism (SNP; pronounced "snip"). There are approximately 10 million SNPs that are common in the human population (i.e., at a frequency of 5% or greater). Because of the recombination patterns in the genome, these SNPs are not all independent; some are in linkage disequilibrium (LD) and are often transmitted together. The recent mapping of this LD, available on the HapMap Project website, has allowed the use of LD between SNPs as a tool in genetic studies. By selecting tag SNPs as proxies for several other SNPs, it is possible to reduce significantly the number of SNPs to be genotyped in a study and thus decrease the costs.

Depending on the nature and location of a sequence difference, genetic variations such as SNP may be silent or may have an influence on the biologic pathway(s) in which the protein product encoded by the gene plays a role. For example, some genetic variations will lead to a difference in the amino acid structure of a protein and disturb its function, whereas others may modulate the levels at which the gene and its protein will be expressed. Furthermore, some of the genetic variations that we have observed with these types of

functional consequences may influence normal phenotypic variation (e.g., height, hair color), whereas others may influence clinical phenotypes and thus be considered as risk factors. Certain genetic risk factors modulate an individual's risk to develop disease; others modulate the ability to respond to a given medication or the propensity to develop specific side effects in response to therapy. It is these latter two issues that are considered within the context of pharmacogenomic studies.

Traditionally, genetic traits have been categorized as monogenic or polygenic. In a monogenic trait, the phenotype observed can be explained by variations in a single gene. Cystic fibrosis, sickle cell disease, and Huntington's disease are example of monogenic disorders. Conversely, polygenic traits are expressed through the interactions of several genes and are also influenced by the environment; these are commonly named complex traits. Many complex disorders exist such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), and type 1 diabetes (T1D). CVDs are among the most prevalent complex disorders. Height, skin color, and IQ are also in the complex trait category as are responses to medications, because several factors influence drug pharmacokinetics and pharmacodynamics. Thus, the field of pharmacogenomics tackles the challenge of identifying the drug genes using strategies similar to those used in the search for complex disorders genes.

GENETIC ASSOCIATION STUDIES

Several recent scientific advances have dramatically changed our ability to examine genetic variation as it relates to human disease. The first key advance is the complete determination of the final sequence of the human genome. This advance has provided a direct means to connect a chromosomal region with its DNA sequence and gene content. The second key advance is the successful effort to define DNA sequence variation in the human genome. Specifically, a genome-wide SNP map has grown from an initial version in 1998,[13] with 4000 SNPs, into a current map of approximately 10 million SNPs (www.ncbi.nlm.nih.gov/SNP). The third key advance is the definition of the long-range extent of LD among SNPs in the human genome and the identification of common recombination hot spots that punctuate the extent of LD into so-called haplotype blocks across the genome.[14,15] These advances have facilitated the search for complex trait genes.

Identifying the actual causal gene(s) and causal variant(s) for any given disorder is an important challenge. The most widely used strategy to locate the genes causing a complex trait is association testing because it is the most powerful approach for this purpose.[16] Several genetic variations have been associated with cardiovascular phenotypes or risk factors (Table 10-1).[17-39] Genetic association studies seek evidence for a statistically significant association between the

TABLE 10–1 Genes Associated with Cardiovascular Phenotypes and Risk Factors

Source (Year)	Gene	Chromosome	Phenotype
Willer et al (2008)[17]	*ABCA1*	9q31	CAD, lipid concentration
WTCCC (2007)[18]	*ADAMTS7*	15q25	CAD
Helgadottir et al (2004)[19]	*ALOX5AP*	13q12	Myocardial infarction
Diabetes Genetics Initiative; Saxena et al (2007)[20]; Willer et al (2008)[17]	*APOA5*	11q23	Triglyceride; CAD, lipid concentration
Kathiresan et al (2008)[21]	*APOB*	2p24	Lipid concentration (LDLs, high-density lipoproteins [HDLs], triglycerides)
Fredriksson et al (2007)[22]	*APOE*	19q13	CVD
Willer et al (2008)[17]	*APOC1-APOC4-APOC2* cluster	19q13	CAD, lipid concentration
Ozaki et al (2009)[23]	*BRAP*	12q24	Myocardial infarction
Scott et al (2007)[24]; Zeggini et al (2007)[25]	*CDKAL1*	6p22	Type 2 diabetes
McPherson et al (2007)[26]; Scott et al (2007)[24]; WTCCC (2007)[18]; Zeggini et al (2007)[25]	*CDKN2A/B*	9p21	CAD
Kathiresan et al (2008)[21]	*CELSR2, PSRC1, SORT1*	1p13	Lipid concentration (LDL, HDL, triglycerides)
Diabetes Genetics Initiative; Saxena et al (2007)[20]	*CETP*	6q13	Lipid concentration (HDL, triglycerides)
Vasan et al (2007)[27]	*CFTR*	7q31	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses
Pare et al (2007)[28]	*EDN1*	6p24	CAD, HDL
Vasan et al (2007)[27]	*FAM5C*	1q31	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses
Kathiresan et al (2008)[21]	*GALNT2*	1q42	Lipid concentration (LDL, HDL, triglycerides)
Diabetes Genetics Initiative; Saxena et al (2007)[20]	*GCKR*	2p23	Triglycerides
Willer et al (2008)[17]	*GCKR*	2p23	CAD, lipid concentration

TABLE 10–1 Genes Associated with Cardiovascular Phenotypes and Risk Factors—Cont'd

Source (Year)	Gene	Chromosome	Phenotype
Vasan et al (2007)[27]	*KCNB2*	8q13	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses
Willer et al (2008)[17]	*LDLR*	19p13	CAD, lipid concentration
Diabetes Genetics Initiative; Saxena et al (2007)[20]	*LIPC*	15q22	Triglycerides
Kathiresan et al (2008)[21]; Willer et al (2008)[17]	*LPL*	8p21	Lipid concentration (LDL, HDL, triglycerides), CAD
Helgadottir et al (2006)[29]	*LTA4H*	12q23	Myocardial infarction
Erdmann et al (2009)[30]	*MRAS*	3q22.3	CAD
Samani et al (2007)[31]	*MIA3*	1q41	CAD
Myocardial Infarction Genetics Consortium; Kathiresan et al (2009)[32]	*MRPS6-SLC5A3-KCNE2*	21q22	Myocardial infarction
Samani et al (2007)[31]	*MTHFD1L*	6q25	CAD
Arking et al (2006)[33]	*NOS1AP*	1q23	QT interval
Dahlman et al (2007)[34]	*NPFFR2*	4q13	Leanness and increased lipolysis
Vasan et al (2007)[27]	*OBFC1*	10q24	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses
Cohen et al (2006)[35]	*PCSK9*	1p32	CAD, LDL concentration
Myocardial Infarction Genetics Consortium (2009)[32]	*PHACTR1*	6p24	Myocardial infarction
Samani et al (2007)[31]; Sandhu et al (2008)[36]	*PSRC1*	1p13	CAD, LDL cholesterol concentration
Gudbjartsson et al (2009)[37]	*SH2B3*	12q24	Myocardial infarction
Tregouet et al (2009)[38]	*SLC22A3-LPAL2-LPA*	6q26-q27	Myocardial infarction
Li et al (2007)[39]	*SLC2A9*	4p16	Serum uric acid level
Vasan et al (2007)[27]	*SLIT2*	4p15	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses
Samani et al (2007)[31]	*SMAD3*	15q22	CAD
Kathiresan et al (2008)[21]	*TBL2*	7q11	Lipid concentration (LDL, HDL, triglycerides)
Sandhu et al (2008)[36]	*TOMM40*	19q13	LDL cholesterol concentration
Myocardial Infarction Genetics Consortium; Kathiresan et al (2009)[32]	*WDR12*	2q33	Myocardial infarction
Vasan et al (2007)[27]	*WRN*	8p12	Echocardiographic dimensions (left ventricle); brachial artery endothelial function; treadmill exercise responses

marker allele and a disease at the population level. Specifically, the association approach involves comparing the frequency of an allele at the marker locus between a sample of unrelated affected individuals and an appropriate, well-matched control sample that is representative of the allelic distribution in the general population. In the context of pharmacogenomics, a group of responder patients is compared with a group of nonresponder patients. Alternatively, the association of a SNP of interest and a continuous trait (e.g., blood pressure, cholesterol) can be investigated. Testing for association to disease is direct (testing the actual mutation) or indirect (testing a genetic variant that acts as a proxy for the mutation). It usually follows one of two common study designs, candidate gene testing or unbiased genome-wide association mapping (Fig. 10-1).

Three main factors that directly influence the success of association studies are the size of the cohorts under study, matching of the different groups, and replication of the discovered association. Traditionally, collections of patients (or cases) and unrelated matched controls were tested for differences in allele frequencies. Initially, association-based genetic studies were generally limited to the testing of modestly sized cohorts of patients with a small number of genetic variants in one gene or in a small number of genes. Unfortunately, this led to a very large number of false-positive results. Today, given the focus on complex traits and the modest effects of individual genes, study design generally involves hundreds to thousands of samples; meta-analyses (i.e., combining the data of several independent studies) are becoming more popular and allow the identification of very modest effects of genes. One other major source of error in case-control studies is that of inadequate matching—that is, differences between the case and control populations that are unrelated to disease, also known as stratification. Careful selection of samples and corrections for stratification are now integrated into association study designs. In addition, replication of the association signals is essential to eliminate false-positive associations. Most studies are designed as two-stage experiments, with

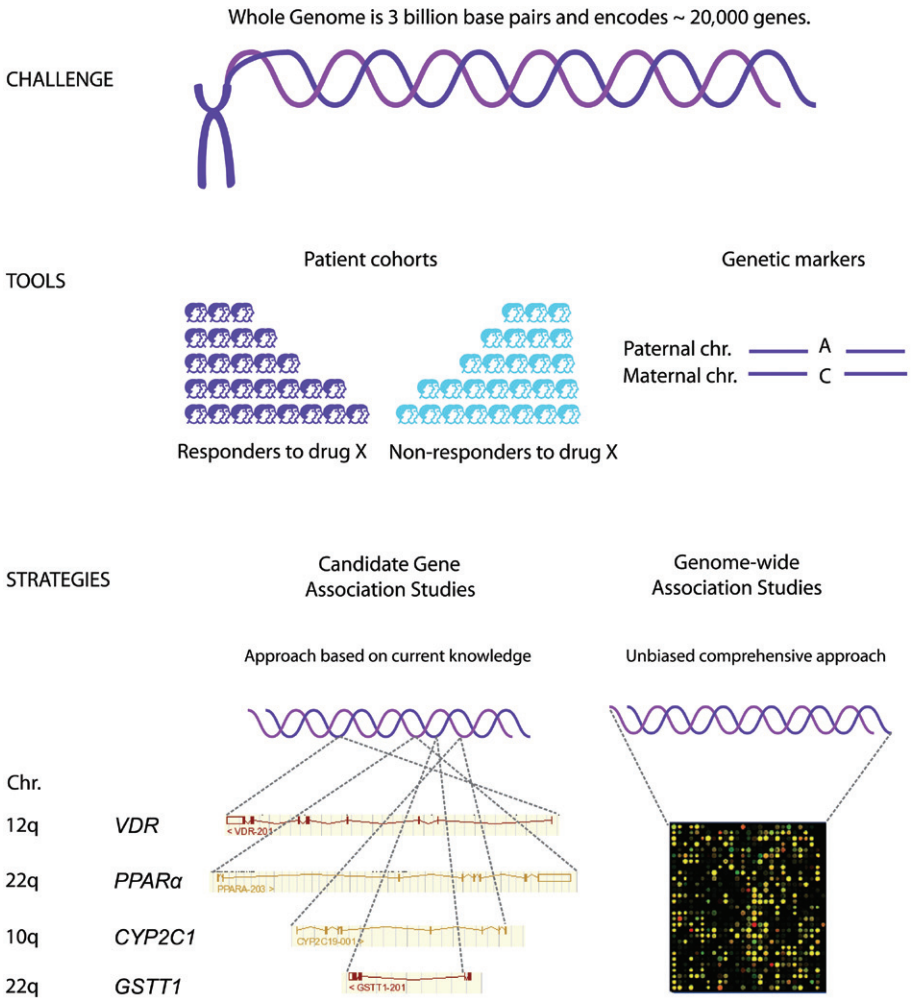

FIGURE 10–1 Identifying a susceptibility gene in the context of a clinical trial. The human genome consists of a four-letter code, 3 billion letters long, and is found in each cell in the shape of chromosomes. Approximately 0.3% of these letters are variable and are called SNPs. The challenge is to identify which of these control response to medication. Just like in a complex trait, the interactions among several genes are responsible for the response to medication. The individual risk conferred by each specific susceptibility gene is usually low. As a result, these genes are usually harder to identify than genes causing a monogenic disorder. However, geneticists have developed tools and strategies to search among the ~20,000 genes of the genome. The most common way is to compare the allelic frequencies of genetic markers (e.g., SNPs) between two groups (such as responders to a particular drug and nonresponders). If the frequency is significantly different, it means that the marker allele, and thus the gene within which the marker is located, is associated to the studied trait (e.g., response to drug X). Two main strategies coexist, the candidate gene approach and the GWA approach. In the candidate gene approach, genes are selected through literature searches according to their functions and presumed involvement in the biologic pathways under study (e.g., drug-metabolizing genes). Markers in these genes are then tested for association to the trait. Typically, less than 100 markers are genotyped per study and most of these SNPs are in the protein-coding region of the genes. In the GWA approach, no gene selection is needed. Actually, millions of genetic markers covering the entire genome are tested for association. This relatively new strategy has led to the discovery of several previously unsuspected susceptibility genes.

large cohorts for both stages. The first stage is for screening to detect associations and the second stage is for replication. More details concerning the limitations of association testing (i.e., statistical design, evaluation of the candidate gene, ethnic variability in disease susceptibility) as well as methods to detect and correct for stratification have been described in detail elsewhere.[40,41]

Candidate Gene Approach

The candidate gene approach relies on selecting genes based on knowledge of their biologic function as likely to have an influence on disease susceptibility, and testing the known genetic variants in and around the gene for association to disease.[42] The number of SNPs tested in such study, up to a few thousand, keep the cost of this strategy relatively low compared with the genome-wide alternative. For example, the role of apolipoprotein E in the metabolism of cholesterol and triglycerides made it a central candidate for CVD risk and its implication has been confirmed in several association studies.[43] Unfortunately, of the approximately 20,000 genes that are believed to exist in the human genome, few have been annotated for specific function. Moreover, it is not that uncommon for functional annotation of genes to be

TABLE 10–2 Genes Possibly Associated with Responses to Drugs

Source (Year)	Gene	Chromosome	Gene description	Drug
Pharmacokinetics				
Ismail and Teh (2006)[45]; Kirchheiner et al (2007)[46]	*CYP2D6*	22q13	Cytochrome P-450 2D6	Metoprolol, carvedilol, flecainide, propafenone, codeine
Sconce et al (2005)[47]; Limdi et al (2008)[48]; Schwarz et al (2008)[49]	*CYP2C9*	10q24	Cytochrome P-450 2C9	Warfarin, irbesartan, losartan
Collet et al (2009)[50]; Mega et al (2009)[51]; Sibbing et al (2009)[52]	*CYP2C19*	10q24	Cytochrome P-450 2C19	Clopidogrel
Zheng et al (2003)[53]; Wilke et al (2005)[54]	*CYP3A5*	7q22.1	Cytochrome P-450 3A5	Atorvastatin, simvastatin, lovastatin, tacrolimus
Drug Transporters				
Pasanen et al (2006)[55]; Link et al (2008)[56]	*SLCO1B1*	12p	OATP1B1	Pravastatin, simvastatin, rosuvastatin
Pharmacodynamics/Disease-Modifying Gene				
McNamara et al (2004)[57]; Bhatnagar et al (2007)[58]	*ACE*	17q23	Angiotensin-converting enzyme	RAAS inhibitors, blockers
Terra et al (2005)[59]; Liggett et al (2006)[60]	*ADBR1*	10q24	β_1-adrenergic receptor	Beta blockers
Kaye et al (2003)[61]; Lanfear et al (2005)[62]	*ADBR2*	5q31	β_2-adrenergic receptor	Beta blockers
Kurland et al (2002)[63]	*AGT*	1q42	Angiotensinogen	RAAS inhibitors, blockers
Kurland et al (2002)[63]	*AGTR1*	3q21	Angiotensin II receptor, type 1	RAAS inhibitors, blockers
Mackenzie et al (2005)[64]; Li et al (2006)[65]	*ALDH2*	12q24	Aldehyde dehydrogenase	Nitroglycerin
Gerdes et al (2000)[66]; Chiodini et al (2007)[67]	*APOE*	19q13	Apolipoprotein E	Statins
Medina et al (2008)[68]	*HMGCR*	5q13	3-hydroxy-3-methylglutaryl coenzyme A reductase	Statins
Goodman et al (2007)[69]	*ITGB3 (GPIIIa)*	17q21	Integrin β_3	Aspirin
Iakoubova et al (2008)[70]; Iakoubova et al (2008)[71]	*KIF6*	6p21	Kinesin-like protein 6	Statins
Lynch et al (2008)[72]	*NPPA*	1p36	Atrial natriuretic peptide precursor	Antihypertensive agents
Moore et al (2007)[73]	*REN*	1q32	Renin	Aliskiren
Sconce et al (2005)[47]; Schwarz et al (2008)[49]	*VKORC1*	16p11	Vitamin K epoxide reductase	Warfarin

incomplete. One recent example is that of the nicotinic acetylcholine receptor α7 subunit. The main function of the nicotinic acetylcholine receptor family was initially believed to be the transmission of the signals for the neurotransmitter acetylcholine at the neuromuscular junctions; more recently, it was shown to be an essential regulator of the inflammatory response.[44] Many genes related to the pharmacokinetics and pharmacodynamics of drugs are the subject of candidate gene studies (Table 10-2).[45-73] However, candidate gene studies are often unsuccessful. This outcome is not that surprising, given the low likelihood that an investigator could select the few causal genes from the human genome, even armed with the best knowledge of disease pathogenesis. Inadequate sample size has also contributed to this lack of success.

Genome-Wide Association Approach

Most recently, with the development of genotyping platforms that allow the testing of hundreds of thousands of SNPs in parallel, the analytic strength of association studies has been applied in a genome-wide fashion. The early application of this new technology has already resulted in the identification of novel loci for many CVDs and related traits (see Table 10-1) and has revealed a number of biologic pathways and pathogenic mechanisms not previously identified by linkage, candidate gene, or physiologic or animal studies. This demonstrates that genome-wide association (GWA) studies can take an unbiased look at the genome and identify previously unrecognized mechanisms of pathogenesis.

GWA allows interrogation of the common genetic variation across the entire human genome in an unbiased manner. Although it is possible that the causal genetic variant is included in the set of variants or markers tested, the premise for this approach is that one or more of the variants tested will serve as a proxy for the causal variant. This is because genetic variants that are in relatively close proximity to one another are often inherited together, a phenomenon known as LD; this approach is sometimes referred to as LD mapping.[74] Specifically, the information generated by the International HapMap Project has detailed the correlation and patterns between the SNPs in the human genome.[75] This approach is most effectively carried out in a hierarchic fashion, whereby once a significant association signal is detected, additional markers in the vicinity are tested in an attempt to refine the signal, hopefully down to a single gene. Crohn's disease is one of the most studied complex traits and numerous GWA studies have yielded satisfying, but also surprising, discoveries, implicating previously unsuspected pathways.[76] The effect size of the DNA polymorphisms associated with complex human diseases is small, and thus the major determinant in the identification of new genetic risk factors for complex disease by GWA studies has been the number of patients and controls genotyped. This is exemplified most convincingly by the progress made in the study of the genetics of Crohn's disease. Four initial GWA studies scanned 547, 547, 946, and 1748 patients with Crohn's disease and identified eight new risk loci; with the three previously reported associations (*NOD2*, IBD5, and *TNFSF15*), this brought the total of risk loci for Crohn's disease to 11.[75] In a large meta-analysis of three of these groups' association results, Barrett and colleagues have reported the identification of an additional 21 new loci, bringing the total of Crohn's-associated susceptibility loci to 32.[76a]

Recently, several independent GWA studies on CAD susceptibility have been undertaken. In these studies, a genetic locus located on chromosome 9q21, which is near the tumor

suppressor genes *CDKN2A/B*, was consistently associated with the risk of CAD.[18,26,31,77,78] Apart from the 9p21 locus, several genes have been associated with CAD following GWA studies (GWAS), including the recently identified *SLC22A3-LPAL2-LPA* and *MRAS*[38,79] (see Table 10-1 for a list of known CAD susceptibility genes). Furthermore, because CAD risk factors are themselves heritable complex diseases, a considerable number of GWAS have also been performed to identify their genetic risk factors. Tremendous success was achieved in identifying genetic factors associated with diabetes and concentrations of the different components of the lipid profile (high-density lipoproteins [HDLs], low-density lipoproteins [LDLs], triglycerides; see Table 10-1). In contrast, the GWA approach has not been extensively used in cardiovascular pharmacogenomics studies to date, largely because the sample size of published studies would have had only limited statistical power to test hundreds of thousands of SNPs. Nevertheless, the information derived from GWAS will help lead to a new understanding of the molecular pathways involved in the development of CAD and allow the testing of new and potentially more specific therapeutic targets.

PHARMACOKINETICS AND PHARMACODYNAMICS

Absorption, distribution, metabolism, and excretion (ADME) are the four classic components of pharmacokinetics. The absorption of a drug represents its transfer from its site of administration into the bloodstream.[80] When drugs are administered orally, several factors can modulate their absorption through the gut wall. These factors are not only related to the drug administered (physicochemical characteristics of the drug or its formulation), but also to interactions in the gastrointestinal tract with food or other drugs, as well as physiologic factors such as gastrointestinal motility.[81] Recently, it has become apparent that the absorption of a significant number of drugs is influenced by influx and efflux transporters located on the membrane of enterocytes, and by metabolism in the gut wall.[82,83]

Drug distribution is the process whereby a drug is distributed from the systemic circulation into the interstitial and intercellular fluids to reach its target.[80] For certain drugs, active transporters located on cell membranes of tissues, as well as the presence of metabolizing enzymes in these tissues, also influence the amount of drug that reaches the target.

Metabolism and excretion are two processes whereby drugs are transformed and eliminated from the body.[84] Metabolism generally implicates the transformation of a drug into an inactive compound or into more hydrophilic compounds, which are more easily eliminated by the kidneys. Exceptions include the transformation of a prodrug into an active moiety or the formation of a toxic metabolite. For a drug administered orally, metabolism, both in the gut wall and by the liver, can have a significant impact on the amount of drug that can reach the site of action of the drug (the bioavailability of the drug). Bioavailability should not be confused with absorption. Although absorption is a critical determinant of bioavailability, the latter represents the fraction of the dose administered that reaches the systemic circulation; it also depends on the amount of drug metabolized by the liver or excreted in the biliary tract before reaching the systemic circulation (the first-pass effect).

Enzymes involved in the metabolism of drugs have typically been classified as phase I or II enzymes.[85] Phase I transformation implicates the introduction of a functional group by reactions of oxidation, reduction, or hydrolysis.[84] Although these reactions generally have only a modest effect on the water solubility of the drug, they can nonetheless modify its activity significantly. Phase II enzymes produce conjugation reactions (e.g., glucuronidation), which transform drugs into more polar compounds that facilitate their excretion. Although the liver is the most important organ implicated in drug metabolism, other tissues such as the small intestine have significant metabolizing capacities and can therefore influence the pharmacokinetics of a drug. Metabolism in the target tissue can further alter the amount of drug available to reach the therapeutic target or that can cause an ADR.[86] Finally, although the kidneys are responsible for most drug excretion, it is important to highlight that the biliary tract is also involved in the excretion of a significant number of drugs.

Current data suggest that genetic factors can influence all components of ADME. This illustrates how complex the contribution of genetic variations to drug effects may be, particularly when considering that genes related to the pharmacodynamics of drugs and disease-modifying drugs are also likely contributors to intersubject variability in drug response.

Cytochrome P-450

Cytochrome P-450 (CYP450) are a superfamily of enzymes of major importance. They are responsible for the oxidative metabolism of 80% of drugs and for almost 50% of the overall metabolism of commonly used drugs.[85] They are expressed in the liver and in a number of other tissues, such as the heart, vasculature, intestines, and kidneys.[87] These isoenzymes have been the focus of extensive pharmacogenetic research. Moreover, CYP450s are implicated in an important number of physiologic processes, including aldosterone synthesis (CYP11B2, or aldosterone synthase) and arachidonic acid metabolism (CYP2J2), making them candidate genes for CVD.

Although current data suggest that CYP450 genetic variants may eventually be useful for the clinical use of medications metabolized by these enzymes, no CYP450 genetic test is currently recommended by professional organizations to individualize dosing in the treatment of CVD. Nonetheless, warfarin genotype-based prescribing is likely to become a reality in the near future. Genetic variants of *CYP2C9*, which metabolizes the most pharmacologically active enantiomer of warfarin, S-warfarin, have consistently been associated with warfarin dosing requirements.[88-90] Prospective randomized trials are underway to evaluate the clinical impact of warfarin dosing strategies based on genotype.

Drug Transporters

Investigators have recently also turned toward drug transporters to explain interindividual differences in drug response.[82] These transporters modulate the uptake or efflux of numerous drugs.[81] Because the transporters are present in various tissues, including the gut, liver, biliary tract, and kidneys, the genetic variations of these transporters are expected to influence the absorption, distribution, metabolism, and excretion of drugs. Moreover, given the diversity of these transporters in tissues, a complex interplay between transporters and local metabolizing enzymes may contribute to intersubject variations in drug concentrations in plasma and in tissues.[83]

Two major superfamilies of drug transporters have been described.[82] The first is the solute carrier superfamily (SLC), which can act as facilitated transporters, secondary active transporters, or antiporters.[81] Genetic polymorphisms from the organic anion-transporting polypeptide OATP1B1 coding gene *SLCO1B1* have been proposed to play a significant role in the uptake of statins in the liver, resulting in differences in the efficacy and safety of these drugs.[55,56] The other major family of drug transporters is the adenosine triphosphate

binding cassette (ABC) transporter superfamily.[81,82] One of the first drug transporters identified from this family was the multidrug resistance-1 (MDR1) transporter, also known as P-glycoprotein (PGP), which is encoded by the *ABCB1* gene.[91] This energy-dependent efflux transporter is expressed in a number of tissues, including the gut, kidneys, biliary tract, heart, and brain. Thus, factors modifying the expression of PGP or its activity are expected to influence the pharmacokinetics and pharmacodynamics of its subtrates. This concept has been supported by extensive in vitro and in vivo evidence. For example, mice not expressing PGP have higher plasma concentrations and reduced clearance of PGP substrates such as digoxin and cyclosporine while also demonstrating higher concentrations of these drugs in various tissues, including the brain, kidneys, and heart.[92] In humans, an important number of clinically significant drug interactions are the result of the modulation of PGP expression or activity. The impact of genetic variations of the *ABCB1* gene is currently uncertain, and publication bias has clouded the evaluation of their impact in the literature.[93]

PHARMACOGENOMICS OF DRUGS USED IN THE TREATMENT OF ACUTE CORONARY SYNDROMES

Antiplatelet Agents

The considerable heterogeneity in the degree of platelet inhibition with aspirin, the thienopyridine clopidogrel, and glycoprotein (GP) IIb/IIIa receptor blockers (abciximab, eptifibatide, and tirofiban) has been recognized. This variability has been proposed to have a potential impact on clinical outcome. Patients who have inadequate platelet inhibition with aspirin or clopidogrel have been described as being resistant to these therapies. Although aspirin and clopidogrel resistance remains a subject of debate, as is the definition of these entities, this field of research nonetheless illustrates the important variability of the antiplatelet effect of these agents.

Only limited data have been published regarding the potential role of genetic factors in explaining the pharmacologic effects of GP IIb/IIIa receptor blockers, and previous studies have not provided any clear results. In contrast, numerous genes have been proposed and investigated to explain intersubject variability of response to aspirin (*COX-1*, *GPIa*, *PGIIIa*, *P2Y12*, *P2Y1*). A recent systematic review, however, has found no association between the genetic polymorphisms in these genes and aspirin resistance, except for the *GPIIIa* PIA1/A2 polymorphism, but only in healthy individuals.[69]

For clopidogrel, on the other hand, consistent data support that the *CYP2C19*2* (681 G>A) loss of function variant, and possibly other reduced function variants, is associated with the reduced antiplatelet effects of clopidogrel.[51,94-96] *CYP2C19* is involved in the conversion of clopidogrel into its active metabolite. Clinically, these variants have been associated with poor clinical outcome in many cohorts of patients with existing CAD, including stent thrombosis.[50,52] Given the emerging but conflicting data that some drug interactions with *CYP2C19* inhibitors, such as omeprazole, could significantly influence the efficacy of clopidogrel, future studies should also investigate whether the impact of such interactions varies depending on an individual's genotype and whether these associations are modified by the use of higher maintenance doses of clopidogrel in carriers of the loss of function alleles. Because prasugrel, another thienopyridine, is not influenced by the *CYP2C19*2* genetic polymorphism, it may become an important genetic marker in ACS patients to individualize antiplatelet treatment.

Anticoagulants

Only limited pharmacogenomic data are available for anticoagulants commonly used in the treatment of an ACS (heparin, low-molecular-weight heparins, bivalirudin, fondaparinux). Interestingly, some studies have proposed genetic predictors of heparin-induced thrombocytopenia.[97] Given the dramatic consequences of this ADR, such genetic risk factors could be useful to identify patients who should be treated with agents that do not induce this ADR, such as bivalirudin. The replication of these findings is necessary.

Oral anticoagulants are one of the most widely prescribed class of medications in the Western world; the most frequently prescribed is warfarin. Warfarin therapy, however, is greatly complicated by the drug's narrow therapeutic index and by the extensive interindividual variability in the daily dose required to attain a therapeutic response, with 5% of patients prescribed doses of 10 mg or more.[98] Traditional warfarin dosing algorithms rely on trial and error dose adjustments and typically require several weeks of monitoring to reach a stable dose to maintain a targeted prothrombin time using the international normalized ratio (INR). Patients who are underdosed are at risk of life-threatening thrombosis, whereas those who are overdosed are at risk of severe bleeding and possibly death. Literature reports of major bleeding frequencies for warfarin vary, to as high as 16%.[99]

Despite these issues, these agents are extensively used for the prevention of thromboembolic events in patients with a clinical history of deep vein thrombosis, atrial fibrillation, mechanical heart valve prostheses, recurrent stroke, or pulmonary embolism. Clinical trials have also demonstrated the efficacy of oral anticoagulants in the secondary prevention of a myocardial infarction (MI) compared with or in addition to aspirin. Because of the complex management associated with their use, professional organizations have not recommended them as the preferred antiplatelet or anticoagulant strategy in the secondary prevention of ACS or MI.[100] Nevertheless, for patients who have experienced an MI, they are recommended in the presence of left ventricular dysfunction and extensive regional wall motion abnormalities and for patients who present with a thrombus in their left ventricle.

One of the most common dosing strategies for warfarin is to prescribe 5 mg/day and adjust the dosage based on INR values. This is an inefficient process because there are many factors that can influence a patient's response to an anticoagulant; these include age, gender, ethnicity, body size, diet, concomitant medications, and comorbidities. Recently, a number of studies have identified two major genes that contain genetic differences responsible for a significant portion of the pharmacogenomic variability observed in warfarin dosing.[88-90] Common genetic variations have been identified in the CYP450 2C9 (*CYP2C9*) gene. This enzyme is responsible for the metabolism of S-warfarin, the most pharmacologically active enantiomer of warfarin. If a person lacks this enzyme activity, lower doses of warfarin are required and the patient is at risk of being overanticoagulated, putting him or her at a higher risk of bleeding.[101] Approximately 2% to 6% of whites have been identified as having poor metabolic activity in the *CYP2C9* gene (most *CYP2C9*2* and **3* alleles). The other gene is the vitamin K epoxide reductase complex gene (*VKORC1*), which binds warfarin and inhibits the induction of the vitamin K cycle (Fig. 10-2).[102] Inhibition of *VKORC1* results in anticoagulation through the reduction in the synthesis of coagulation factors II, VII, IX, and X. Variations within the *VKORC1* gene have been identified that result in differences in the expression levels of this protein, which can change the pharmacodynamic response of warfarin. Patients who possess a variant SNP in the promoter region of this gene (*VKORC1* G3673A; -1639 G→A) will require less warfarin to achieve a target INR.[103] An additional significant gene effect

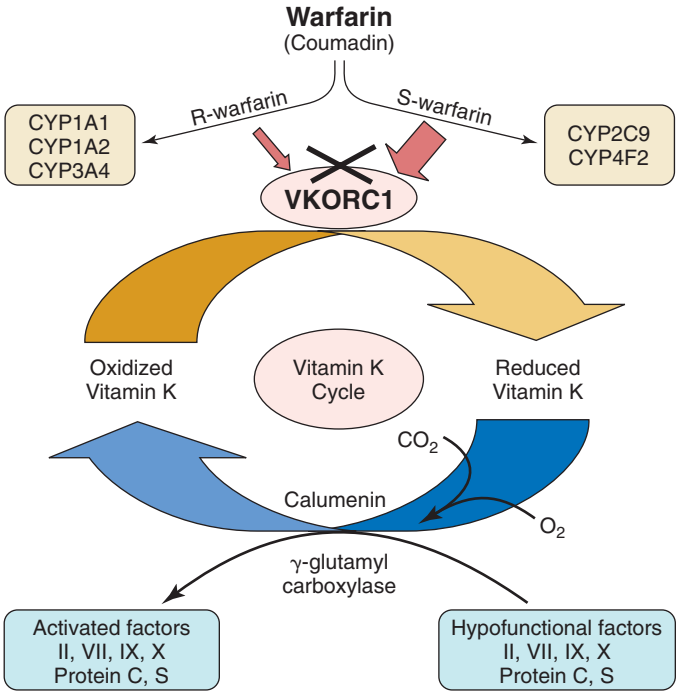

FIGURE 10–2 Schematic diagram of the vitamin K cycle illustrating the pharmacokinetic and pharmacodynamic pathways of warfarin. Warfarin is administered as a racemic admixture of R- and S-enantiomers. The more potent S-enantiomer is metabolized principally by *CYP2C9* and the recently discovered *CYP4F2* genes. Variation within either of these CYP genes causes reduced activity in their enzymatic activity, resulting in higher circulating drug levels and longer times until the drug is cleared from the body. The pharmacologic effect of warfarin is mediated by the inhibition of the vitamin K epoxide reductase complex 1 gene (*VKORC1*). This results in decreased concentrations of activated clotting factors (II, VII, IX, and X) producing therapeutic anticoagulation. Variations within the *VKORC1* gene can result in varying degrees of expression of the warfarin "receptor," leading to differences in receptor number among individual patients. With the advent of pharmacogenomics, the screening of these known pharmacokinetic and pharmacodynamic factors has the potential to help predict a patient's warfarin dose response, which can greatly improve the safety profile of this medication.

has recently been identified that also plays a role in warfarin metabolism in the cytochrome P450 4F2 (*CYP4F2*) gene.[104] The *CYP4F2* variant (rs2108622; V433M) was associated with warfarin dose in three independent white cohorts and accounted for a difference in warfarin dose of approximately 1 mg/day between CC and TT subjects. Additional genetic studies are ongoing to investigate additional genes in the vitamin K cycle to see how they affect warfarin dosing. Furthermore, several warfarin resistance genes and variants have also been identified, but these are rare.[105]

It has been demonstrated that these two genetic factors alone account for 30% to 35% of the variability in warfarin dosing, whereas clinical factors can only explain 17% to 21% of the variability.[47,106] Dosing algorithms combining genetic and clinical factors can predict up to 55% of the variability in stable maintenance doses. One such algorithm is available (see http://www.warfarindosing.org). With many groups working to develop an effective warfarin dosing algorithm, it is hoped that we may soon have an improved warfarin dosing regimen that reaches a stable maintenance dose of the drug using smaller and fewer dose changes. Inclusion of pharmacogenomic parameters in warfarin dosing also has the potential to reduce hospitalizations by identifying and creating a safer environment for patients at risk of bleeding events. Recent data from a pilot randomized trial support the potential benefits of genotype-based prescribing of warfarin.[107]

Fibrinolytics

In several countries, myocardial reperfusion in the setting of an ST-segment elevation MI is still performed using fibrinolytics such as alteplase (the recombinant form of tissue plasminogen activator [tPA]), tenecteplase, and reteplase; the latter two are obtained from genetic alterations to tPA or the less fibrin-specific streptokinase. It is well established that not all patients respond to these agents, with a TIMI 3 reperfusion rate of 50% to 60% in patients receiving fibrin-specific thrombolytics and approximately 35% with the use of streptokinase. Hence, clinical tools identifying patients most likely to respond to these agents would be of clinical significance, because potential nonresponders and patients at a higher risk of bleeding, in particular intracranial hemorrhage, could preferably be transferred to facilities that can perform primary percutaneous coronary intervention (PCI) or be offered more conservative treatment measures.

Surprisingly, despite the worldwide use of these agents, pharmacogenomic data are extremely limited.[108] Therefore, it is currently difficult to appreciate whether genetic variants can be useful in identifying patients who are most likely to benefit from or are at higher risk of bleeding when these agents are used. Nevertheless, the significant heritability of many factors implicated in coagulation and fibrinolysis suggests that genetic factors may contribute to the intersubject variability of the pharmacologic effects of fibrinolytics.[9,10,109] Plasminogen activator inhibitor-1 (PAI-1), the main inhibitor of endogenous tPA, has constituted a significant focus of research. Many studies have demonstrated an association between plasma concentrations of PAI-1 and the PAI-1 (*SERPINE1*) 4G (four guanine bases)/5G genotype.[110] Whether this genetic polymorphism is a genetic risk factor for CAD remains to be established.[111] Nonetheless, because PAI-1 is the main inhibitor of tPA, this or other variants from this gene could potentially modulate the response to fibrinolytics. Given the complexity of the response to these agents and the importance of demographic factors and parameters related to the severity of the MI, pharmacogenomic studies of fibrinolytics will require large populations to identify genetic predictors of their efficacy and safety.

Nitrates

Nitroglycerin and other nitrates have been used for the treatment of ischemic heart disease for more than 100 years. Although the use of these agents in patients with ACS does not improve survival, nitroglycerin nevertheless remains an important part of the pharmacologic treatment in selected patients to reduce ischemic symptoms, lower blood pressure and improve symptoms of heart failure.

Only limited pharmacogenetic data exist for this pharmacologic class. Recent data have suggested that the mitochondrial aldehyde dehydrogenase gene (*ALDH2*), and more specifically the *ALDH2* Glu504Lys polymorphism, could have a significant role in the bioactivation of nitroglycerin in humans. In a study of patients of Han Chinese ethnicity, patients presenting a normal activity of the enzyme (*ALDH2* Glu504 homozygotes) were more likely to experience an improvement in ischemic symptoms following the administration of sublingual nitroglycerin than carriers of the Lys504 allele.[65] Another study has reported that *ALDH2* Lys504 carriers also experience significantly less vasodilation during the administration of intravenous nitroglycerin.[64]

Because nitroglycerin produces its vasodilatory effects by providing exogenous nitric oxide (NO), SNPs of genes involved in the biosynthesis of endothelium-derived NO could also influence the response to nitroglycerin. Endothelial nitric oxide synthase (*NOS3*) has been the focus of

considerable research. Two *NOS3* genetic polymorphisms have been most widely studied, T786C and Glu298Asp. Although these genetic polymorphisms have been associated with CAD and hypertension in many studies, recent meta-analyses have questioned whether these genetic variants have any implications for the genesis of these diseases and have highlighted the existence of significant publication bias.[112]

Beta Blockers

Given the significant heterogeneity of the response to beta blockers, these agents have constituted an important focus of pharmacogenomic research in patients with hypertension and heart failure. The two most widely studied genes are the *ADRB1* gene, which encodes the β_1-adrenergic receptor, and the *ADRB2* gene, which encodes the β_2-adrenergic receptor.

The most extensively studied adrenergic genetic polymorphism in CVDs is arguably the *ADRB1* Arg389Gly polymorphism. The 389Arg allele is associated with an increased basal production of cyclic adenosine monophosphate (cAMP) compared with the 389Gly allele.[113] Theoretically, the hyperresponder phenotype associated with the 389Arg allele should make carriers of this allele more likely to benefit from beta blockers. Studies in patients with hypertension or heart failure support that this genetic polymorphism is a significant modulator of blood pressure reduction and improvements in left ventricular remodeling produced by beta blockers. The largest published cohort that has evaluated the impact of this genetic polymorphism is the pharmacogenetic substudy of the Beta blocker Evaluation of Survival Trial (BEST), which included 1040 patients.[60] In this substudy, the significant reduction in mortality and hospitalizations with bucindolol was observed only in *ADRB1* 389Arg homozygotes.[60] Carriers of the *ADRB1* 389Gly allele experienced no significant benefit. Because of the unique sympatholytic effect of bucindolol and the absence of mortality benefit in the main study, these data cannot be extrapolated to other beta blockers. In fact, this genetic polymorphism had no impact on the effects of metoprolol succinate in a smaller substudy from the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).[114] To date, only one major study has evaluated the impact of genetic variations on the benefits of beta blockers in patients with ACS. In this study, no significant impact was observed for the *ADRB1* Arg389Gly polymorphism[62]; in contrast, a significant association was observed between the *ADBR2* Gly16Arg and Gln27Glu genetic polymorphisms and mortality in patients treated with a beta blocker.

Emerging data suggest that the *ADR2C* gene, which encodes for the presynaptic α_{2c}-adrenergic receptor,[115] and *GRK5* gene, which encodes for the β-adrenergic desensitizing G protein–coupled receptor kinase-5, can provide additional information to identify patients who are most likely to benefit from these agents.[116] Replication of these findings is required, however. Finally, extensive data support the impact of *CYP2D6* genetic variations on the pharmacokinetics of the beta blockers carvedilol and metoprolol. Limited data have suggested that those variations could also influence tolerability to these beta blockers.[117] Nonetheless, the clinical implications of these variations remain to be established. The lack of consistency between published studies may be attributable to several factors, including insufficient sample sizes. Another important factor is that most of these studies have generally been limited to one or a limited number of SNPs or genes. Given the complexity of the pharmacokinetics and pharmacodynamics of beta blockers, as well as the intricacies of the adrenergic system, future trials should adopt a more comprehensive approach that takes all these variables into consideration.

Renin-Angiotensin-Aldosterone System Inhibitors and Blockers

The clinical benefits of ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists have been demonstrated in multiple cardiovascular populations. Because the renin-angiotensin-aldosterone system (RAAS) has been shown in a number of studies to present considerable heritability,[6,7] genetic polymorphisms should be useful in predicting the response to RAAS inhibitors. Several genetic polymorphisms have been associated with the expression and activity of many components of the RAAS, such as the *ACE* insertion/deletion (I/D) and the *AGT* Met235Thr polymorphisms. Of these, many have been associated with the response to ACE inhibitors, angiotensin receptor blockers, and spironolactone in small pharmacogenetic studies (see Table 10-2). However, findings from these studies have been variable and some larger cohorts have provided more negative results.[118]

The uncertainty concerning the clinical significance of RAAS genetic polymorphisms is well illustrated by the *ACE* I/D polymorphism. This polymorphism, which consists of the presence (I allele) or absence (D allele) of a 287–base pair sequence in intron 16 of the gene predicts approximately 50% of the variability of plasma ACE activity,[119] with the D allele being associated with the highest ACE activity. Despite being the most widely studied genetic polymorphism in CVDs, its clinical impact remains to be established.[120]

Given the complexity of the RAAS and the importance of nongenetic factors on its activity, these inconsistencies in study results could partially be attributable to the fact that many of these studies were limited to the evaluation of one gene (and often one genetic polymorphism) and ignored nongenetic factors such as sodium consumption. Emerging data support the additive effects of multiple genetic polymorphisms[121] and the importance of gene-sodium consumption interaction in association studies implicating RAAS genes.[122] Hence, future pharmacogenomic studies investigating RAAS modulators should include a more comprehensive genotyping approach, as well as the influence of dietary factors. Moreover, given the intricate relationships between the RAAS and other neurohormonal systems, such as the bradykinin-kallikrein and adrenergic systems, genetic variations in these pathways should also be studied in future pharmacogenomic studies.

Statins

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are among the most widely prescribed drugs in the world, with over 150 million prescriptions filled in 2006 in the United States alone. Each of the six currently available statin drugs is regarded as both safe and effective. As a result of millions of patients now being exposed to statin therapy, statin-related complications in the form of nonresponders and patients experiencing severe ADRs have become more numerous and better characterized.[11]

Many studies have been undertaken to investigate potential pharmacokinetic and pharmacodynamic factors that can affect cholesterol-lowering therapies. Several genes have been identified and associated with the pharmacokinetics and efficacy of statins; however, most of the positive associations were described in small studies and failed to be reproduced in larger cohorts.[123] One of the genes that has been shown to predict a positive pharmacodynamic effect for statins is the human apo E gene which is defined by three alleles—ε2, ε3, and ε4.[43,124] Several studies have shown that the decrease in low-density lipoprotein (LDL) cholesterol in response to statin therapy is impaired in patients with at least one apo ε4 allele, and that the apo ε2 allele is more frequent in

responders,[125-127] but current data suggest that high-risk apo ε4 carriers experience the greatest reduction in cardiovascular events.[66,128] More recently, a novel protease, proprotein convertase subtilisin/kexin type 9 (PCSK9), has been identified, which mediates degradation of the LDL receptor; patients with gain of function mutations have been associated with increased LDL cholesterol levels and an attenuated statin response.[129,130]

In patients on statin therapy, LDL cholesterol response is variable and influenced by many factors, including ethnic factors, with attenuated responses often being observed in African Americans. Specifically, CYPP450 3A5 (*CYP3A5*) genotypes have been associated with altered lipid-lowering responses to lovastatin, simvastatin, and atorvastatin. The observed statin response was significantly lower in *CYP3A5*1* carriers (*CYP3A5* expressors) because of a higher rate of clearance as compared with *CYP3A5*3* homozygotes (*CYP3A5* nonexpressors).[131] Because the *CYP3A5* expressor phenotype is predominant in African Americans and only present in 10% of whites, it should be considered as a genetic contributor to interindividual and interethnic differences when using statins. Furthermore, an alternative splicing polymorphism has recently been identified that is located in exon 13 of the HMG-CoA reductase gene.[68] This polymorphism has been associated with interindividual variation in plasma LDL cholesterol response to statin treatment. A SNP (rs3846662) primarily found in African Americans was associated with reduced statin sensitivity and was a determinant of interindividual differences in LDL cholesterol, apolipoprotein B, and triglyceride levels in response to statin treatment.[68] An example of a gene that is a risk factor for CAD but that can modify statin response is the kinesin family member 6 gene (*KIF6*). Recent data have associated a SNP in the *KIF6* gene with a change of Trp719 to Arg, which has been shown to be associated with an increased risk of coronary heart disease and MI. In the CARE and WOSCOPS pharmacogenomics substudies, high-risk patients having the 719Arg allele derived the greatest benefit from pravastatin.[70] Furthermore, data from the PROVE IT-TIMI 22 trial have demonstrated that these patients also experience the greatest benefit from high-dose atorvastatin following an ACS.[71] Hence, the *KIF6* Trp719Arg genetic polymorphism represents another candidate marker that can be used to select patients who will benefit the most from statin therapy.

One of the most striking adverse effects of the use of statins is musculoskeletal complaints. This muscle toxicity, commonly manifested clinically as isolated muscle pain, often causes patients to alter their course of therapy. The most extreme manifestation of statin-induced muscle toxicity is rhabdomyolysis. In general, the incidence of rhabdomyolysis is extremely low.[11,132] A review of more than 250,000 records of patients treated with atorvastatin, pravastatin, or simvastatin has revealed that rhabdomyolysis was reported at an incidence of 0.000044 events/person/year in those receiving monotherapy.[11,132] Statin-induced muscle complications appear to be dose-dependent. For this reason, membrane transporters have long been hypothesized to contribute to a variety of statin-related clinical outcomes. Polymorphisms in candidate solute transporter genes (e.g., the solute carrier organic anion transporters family member 1B1 gene [*SLCO1B1*, also known as *OATP-C*]) have been associated with altered hepatic uptake of pravastatin.[133] Recently, the SEARCH group has identified common variants in the *SLCO1B1* gene that are strongly associated with an increased risk of statin-induced myopathy with the use of simvastatin.[56] Additional studies are currently ongoing to replicate this finding in simvastatin-treated patients and to investigate its applicability to other statin family members. Moreover, there are currently many international research efforts focused on identifying additional genes that contribute to statin-induced myotoxicity. With all this new information being uncovered about statin pharmacogenomics, it is hoped that in the future patients will benefit from improved screening to achieve better safety and efficacy of lipid-lowering therapy.

In conclusion, although no genetic test is currently used for the treatment of CVD, accumulating data suggest that genotype-based prescribing lies not far ahead, particularly in the case of warfarin. Nonetheless, in recent years, many have highlighted the inconsistencies in results of genomic and pharmacogenomic studies that may transform the hope of personalized medicine into an unmet "hype." Hence, minimizing the factors responsible for these inconsistencies will be vital in future studies. More specifically, future studies should be adequately powered. Second, individuals and drug responses should be carefully phenotyped. Third, nongenetic factors such as diet should be assessed and their impact considered. Fourth, in case-control studies, controls should be carefully selected based on detailed demographic characteristics and phenotypic information, and not primarily on the availability of DNA samples. Although considerable efforts and progress have been made in recent years to improve technologies that now enable the rapid genotyping of millions of SNPs by high-throughput methods, future efforts should be directed at studying large cohorts of extremely well-phenotyped individuals for whom detailed information about nongenetic and environmental factors are collected. Ultimately, these clinical investigations will be responsible for the fulfillment of the promise of individualized medicine to get the right drug at the right dose to the right patient at the right time.

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SECTION III

Patient-Based Perspectives, Diagnosis, and Risk Stratification

CHAPTER 11

Clinical Recognition of Acute Coronary Syndromes

Eugene Braunwald

HISTORICAL PERSPECTIVE

Angina pectoris literally translates as "strangling in the chest." William Heberden presented one of the earliest descriptions of angina pectoris in 1768 in a lecture to the Royal College of Physicians. In it, he described the classic symptoms of angina[1]:

> *This is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it . . . . The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly called angina pectoris . . . . Those who are afflicted with it are seized . . . with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or continue . . . . When a fit of this sort comes on by walking, its duration is very short, as it goes off almost immediately upon stopping. If it comes on in the night, it will last an hour or two.*

The clinical syndrome accompanying acute myocardial infarction was described by two Russian physicians, Obrastzov and Strazhesko in 1910,[2] and then by William Herrick in 1912.[3]

In 1937, Sampson and Eliaser[4] and Feil[5] published separate but remarkably similar case series describing a syndrome intermediate between chronic stable angina and acute myocardial infarction, which they termed *impending acute coronary occlusion*. Sampson and Eliaser wrote that "The character of the premonitory attack of precordial pain observed in these patients . . . rarely differed from their former pain either in its nature—i.e. squeezing, crushing—or in radiation. The effect of nitroglycerin on the premonitory attack was definitely transient, with failure of complete relief even on repeated doses . . . ."[4]

Multiple terms for this syndrome proliferated in the literature, including *preinfarction angina*, *accelerated angina*, *acute coronary insufficiency*, and *intermediate coronary syndrome*. In 1971, Fowler first used the term *unstable angina*, which he defined[6] as the

> *. . . sudden onset of one or more anginal attacks a day from a previous background of good health or . . . a dramatic change in the symptomatic pattern of previously recognized coronary disease . . . . In patients with unstable angina, the attacks, in addition to being more frequent, are also often of longer duration and may occur at rest without an apparent precipitating event . . . . The electrocardiogram shows no evidence of recent infarction, and such serum enzymes as the glutamic oxaloacetic transami-*

TABLE 11–1 Braunwald Clinical Classification of Unstable Angina and Non–ST-Elevation Myocardial Infarction

Class	Definition	Death or MI to 1 Yr (%)*
Severity		
Class I	New onset of severe angina or accelerated angina; no rest pain	7.3
Class II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	10.3
Class III	Angina at rest within 48 hr (angina at rest, subacute)	10.8†
Clinical Circumstances		
A (secondary angina)	Develops in the presence of extracardiac condition that intensifies myocardial ischemia	14.1
B (primary angina)	Develops in the absence of extracardiac condition	8.5
C (postinfarction angina)	Develops within 2 wk after acute myocardial infarction	18.5‡
Intensity of treatment	Patients with unstable angina may also be divided into three groups, depending on whether unstable angina occurs: (1) in the absence of treatment for chronic stable angina; (2) during treatment for chronic stable angina; or (3) despite maximal anti-ischemic drug therapy. These three groups may be designated with subscripts 1, 2, and 3, respectively.	
ECG changes	Patients with unstable angina may be further divided into those with or without transient ST-T wave changes during pain.	

*Data from Scirica BM, Cannon CP, McCabe CH, et al; Thrombolysis in Myocardial Ischemia III Registry Investigators: Prognosis in the thrombolysis in myocardial ischemia III registry according to the Braunwald unstable angina pectoris classification. Am J Cardiol 2002;90:821-826.

†$P = .057$

‡$P < .001$.

nase or the creatine phosphokinase show no diagnostic alterations.

The term *acute coronary syndrome* was introduced by Fuster and colleagues in 1985 to highlight the common pathophysiologic link that distinguishes unstable angina (UA) and acute myocardial infarction from chronic stable angina. An important distinction was made[7] between the fact that

. . . the early and some of the advanced coronary atherosclerotic lesions progress very slowly, . . . [while] some of the advanced coronary atherosclerotic lesions progress very rapidly, probably by means of complicating anatomic events, one of which is related to a thrombogenic process . . . . These complicated processes appear to be of paramount importance in the pathogenesis of some of the acute coronary syndromes including unstable angina, myocardial infarction, and sudden coronary death.

In 1989, I proposed a clinical classification of UA to "separate patients with unstable angina into a manageable number of meaningful and easily understood subgroups based on the severity, the presumed precipitating cause, and the presence of electrocardiographic changes . . . ."[8] According to this classification, patients are divided into three groups (I to III) based on the severity of angina and three groups according to the clinical circumstances in which the acute ischemic episode occurs (A to C). This classification has been shown to correlate both with the severity of coronary disease as assessed by arteriography as well as with early mortality (Table 11-1). From this classification, three principal presentations of unstable angina are recognized (Table 11-2).[8,9]

The acute coronary syndromes comprise a wide spectrum of conditions that includes unstable angina, non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI; Fig. 11-1). Acute coronary syndromes are heterogeneous; their clinical severity ranges from an asymptomatic condition, recognizable only by a change in the electrocardiogram (ECG), to an explosive, life-threatening event. The most common pathophysiologic process that underlies the acute coronary syndromes is rupture or erosion of an unstable atherosclerotic plaque, with subsequent formation of a platelet-fibrin thrombus. Coronary vasospasm and vasoconstriction, progression of atherosclerosis, and increased myocardial oxygen demand in the presence of a fixed, limited supply may also play pathogenetic roles.[10] The degree to which coronary blood flow is impaired, the level of myocardial oxygen demand, the presence or absence of collateral flow, and other patient-specific factors combine to determine the clinical presentation.

CLINICAL SETTING

Most patients who present with an acute coronary syndrome have an antecedent history of angina pectoris, and approximately 80% have a prior history of coronary artery disease. Three fourths of patients with NSTEMI and slightly more than half of patients with UA are male. However, women predominate among the rapidly expanding older population with unstable angina.[11-13]

Acute coronary syndrome has been found to have a circadian periodicity, with the peak incidence occurring between midnight and 6 AM.[14] Acute coronary syndromes can be precipitated by vigorous exercise, particularly in previously sedentary persons. Emotional stress, including that created by natural disasters, may lead to plaque rupture, acute coronary

TABLE 11–2 Three Principal Presentations of Unstable Angina

Class	Presentation
Rest angina*	Angina occurring at rest and prolonged, usually greater than 20 min
New-onset angina	New-onset angina of at least CCS class III severity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by 1 or more Canadian Cardiovascular Society (CCS) class to at least CCS class III severity)

*Patients with NSTEMI usually present with angina at rest.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol 2007;50:e1-e157.

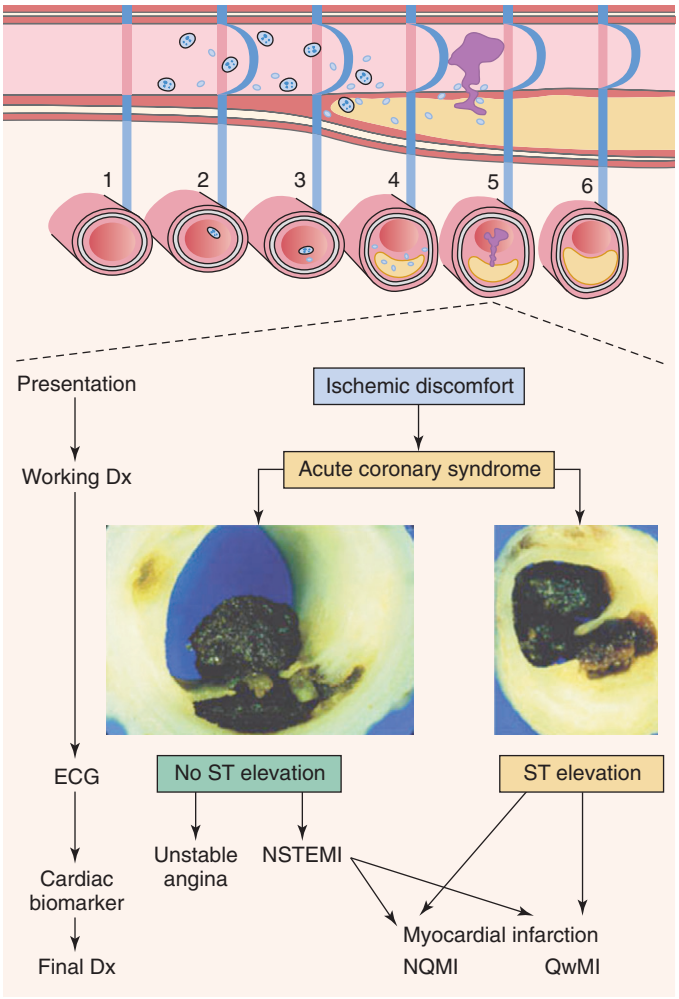

FIGURE 11–1 Acute coronary syndromes. The longitudinal section of an artery depicts the timeline of atherogenesis from a normal artery (1) to lesion initiation and accumulation of extracellular lipid in the intima (2), to the evolution to the fibrofatty stage (3), to lesion progression with procoagulant expression and weakening of the fibrous cap (4). An ACS develops when the vulnerable or high-risk plaque undergoes disruption of the fibrous cap (5); disruption of the plaque is the stimulus for thrombogenesis. Thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth (6). Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery.

The flow reduction may be caused by a completely occlusive thrombus (*bottom half, right*) or subtotally occlusive thrombus (*bottom half, left*). Patients with ischemic discomfort may present with or without ST-segment elevation on the ECG. Of patients with ST-segment elevation, most ultimately develop a Q-wave MI (QwMI), whereas a few develop a non–Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from unstable angina or a NSTEMI, a distinction made on the presence or absence of a serum cardiac marker such as CK-MB or a cardiac troponin. The spectrum of clinical presentations ranging from unstable angina through NSTEMI and STEMI are referred to as the acute coronary syndromes. Dx, diagnosis; CK-MB, MB isoenzyme of creatine kinase. *(From Antman EM, Braunwald E: ST-elevation myocardial infarction: Pathology, pathophysiology, and clinical features. In Libby P, Bonow RO, Mann DL, Zipes D [eds]: Braunwald's Heart Disease, 8th ed. Philadelphia, Saunders Elsevier, 2008, pp 1207-1232.)*

syndrome, and sudden cardiac death.[15] However, most cases of acute coronary syndrome occur in patients with no identifiable trigger.

History

The hallmark of an acute coronary syndrome is ischemic chest pain (Table 11-3). In unstable angina and NSTEMI, the ischemic pain is typically gradual in onset, and may not reach its peak intensity for several minutes. In myocardial infarction, this pain characteristically begins abruptly, is steady, and lasts for more than 30 minutes.[16] In contrast, in unstable angina, the pain frequently waxes and wanes, lasting from a few minutes to as long as but usually less than 20 minutes.[17] Patients frequently describe the pain using terms such as *pressure*, *burning*, *gnawing*, *tightness*, *heaviness* and when severe, *crushing*. These descriptions suggest a visceral rather than a superficial origin. The discomfort ranges from mild to very severe, depending on patient perception and the mass of myocardium that is ischemic or necrotic. Pain caused by ischemia is exacerbated by exertion and may diminish with rest. Chest pain that is fleeting, stabbing in nature, positional, pleuritic, reproduced by palpation, or that persists for days is rarely caused by an acute coronary syndrome.

The pain in an acute coronary syndrome is most commonly located in the center or left of the chest, with radiation to the left shoulder and arm, neck, and jaw (Fig. 11-2).[18] Less commonly, the pain is epigastric, leading the patient (or physician) to mistake it for indigestion. Rarely, ischemic chest pain may be perceived in the right side of the chest or interscapular region. Severe pain that radiates through the chest into the back is more suggestive of aortic dissection than acute coronary syndrome. Pain that the patient can localize by pointing with one finger is rarely ischemic in origin; rather, ischemic pain usually occupies a substantially larger area. The Levine sign (named for Dr. Samuel A. Levine), in which a patient places a clenched fist over the chest while describing the pain, is classically seen in acute myocardial infarction (Fig. 11-3). The differential diagnosis of chest pain according to the location of the pain is shown in Figure 11-4.

Patients with acute coronary syndrome (ACS), particularly acute myocardial infarction (both STEMI and NSTEMI), may have other symptoms, most commonly dyspnea, diaphoresis, nausea, vomiting, and palpitations accompanying the pain. Gastrointestinal symptoms are most commonly seen with ischemia of the inferior rather than the anterior wall. Other symptoms include apprehension or anxiety, syncope, acute heart failure, generalized weakness, and acute mental status changes. Symptoms that do not include chest pain in patients with ACS or are clinically silent occur more commonly among women,[11,12,19] older adults,[20] patients with diabetes mellitus, and those with a history of heart failure. When these symptoms, most frequently dyspnea, occur without chest pain they may be referred to as "angina equivalents." Episodes of silent ischemia may be detected by ambulatory ST-segment monitoring.

Physical Examination

The physical examination of patients with acute coronary syndrome can vary from completely unremarkable to dramatic, depending on the degree and location of the ischemia as well as individual patient factors. The more severe signs described here frequently accompany acute myocardial infarction, including NSTEMI, rather than unstable angina. In the latter, the signs of acute ischemia may be transient and resolve quickly after the ischemia disappears.

Patients with an acute coronary syndrome frequently appear anxious, and many are restless in an attempt to find a comfortable position. Patients may massage their chest. Diaphoresis, occasionally profound, is commonly seen, particularly in inferior infarction. Skin pallor may be evident. The heart rate can be variable, depending on the degree of anxiety, hemodynamic status, location of ischemia, and underlying cardiac rhythm. Commonly, the heart rate is elevated and ventricular premature beats are present. However, inferior ischemia is frequently accompanied by bradycardia.

TABLE 11–3 Cardiovascular Causes of Chest Pain

Condition	Location	Quality	Duration	Aggravating or Relieving Factors	Associated Symptoms or Signs
Angina	Retrosternal region; radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms (left is common)	Pressure, burning, squeezing, heaviness, indigestion	<2-10 min	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical angina (Prinzmetal's) may be unrelated to activity; often early morning	S_4, or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	Usually <20 min	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina, but may be pronounced. Transient cardiac failure can occur.
Myocardial infarction	Substernal and may radiate like angina	Heaviness, pressure, burning, constriction	Sudden onset, 30 min or longer but variable	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting
Pericarditis	Usually begins over sternum or toward cardiac apex and may radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia	Sharp, stabbing, knifelike	Lasts many hours to days; may wax and wane	Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward	Pericardial friction rub
Aortic dissection	Anterior chest; may radiate to back	Excruciating, tearing, knifelike	Sudden onset, unrelenting	Usually occurs in setting of hypertension or predisposition (e.g., Marfan's syndrome)	Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurologic deficit
Pulmonary embolism (chest pain often not present)	Substernal or over region of pulmonary infarction	Pleuritic (with pulmonary infarction) or angina-like	Sudden onset; minutes to <1 hr	May be aggravated by breathing	Dyspnea, tachypnea, tachycardia; hypotension, signs of acute right-sided heart failure, and pulmonary hypertension with large emboli; rales, pleural rub, hemoptysis with pulmonary infarction
Pulmonary hypertension	Substernal	Pressure; oppressive		Aggravated by effort	Pain usually associated with dyspnea, signs of pulmonary hypertension

From Andreoli TW, Bennet JC, Carpenter CCJ, Plum F: Evaluation of the patient with cardiovascular disease. In Andreoli TW, Bennet JC, Carpenter CCJ, Plum F (eds): Cecil Essentials of Medicine, 4th ed. Philadelphia, WB Saunders, 1997, p 11.

Patients with unstable angina are often normotensive. When the pain and/or anxiety are severe, the blood pressure may be elevated as a consequence of adrenergic discharge. In inferior ischemia, hypotension is common because of excess parasympathetic discharge. The administration of nitrates may reduce or abolish the ischemic pain but may intensify hypotension, particularly in the subset of patients with right ventricular ischemia or infarction.

The body temperature is usually normal in patients with unstable angina. In patients with myocardial infarction, fever frequently develops as a nonspecific response to myocardial necrosis. In such patients, the fever is usually low grade, begins within 4 to 8 hours of infarction, and resolves within 4 to 5 days.

In unstable angina, the respiratory rate is most often normal when the patient is pain-free. An elevated respiratory rate may be seen in acute myocardial infarction, either from pain and anxiety or left ventricular dysfunction. The jugular venous pressure is normal or slightly elevated in most patients with acute coronary syndrome. The lungs are usually clear in patients with unstable angina. Moist rales or wheezing may be heard in the presence of acute myocardial infarction complicated by acute left ventricular dysfunction.

Cardiac Examination

Despite severe symptoms and extensive ischemia, the cardiac examination is often remarkably normal in patients with acute coronary syndrome. Abnormalities are more common in those with acute myocardial infarction than in those with unstable angina, but may occur transiently across the spectrum of acute coronary syndrome.

Palpation of the precordium may reveal an abnormal systolic pulsation to the left of the sternum, reflecting a dyskinetic segment of the left ventricle. A palpable presystolic impulse at the apex usually occurs transiently during active ischemia in patients with unstable angina but may be present for several days in patients with myocardial infarction. A soft first heart sound may reflect acute left ventricular dysfunction, or may be heard in the presence of a first-degree atrioventricular block. A fourth heart sound, frequently audible in patients with acute coronary syndrome, is usually heard best between the left sternal border and the apex, and reflects the reduction in left ventricular compliance associated with ischemia. A third heart sound is caused by rapid deceleration of transmitral blood flow during early diastolic filling of the left ventricle and suggests left ventricular systolic dysfunction.

Systolic murmurs are common in patients with acute coronary syndrome. An apical holosystolic murmur usually results from mitral regurgitation, which can be caused by ischemic dysfunction and displacement of the mitral valve apparatus. This murmur may occur transiently during episodes of ischemia. The systolic murmur of tricuspid regurgitation caused by right ventricular ischemia or infarction is heard along the left sternal border and is accentuated by inspiration.

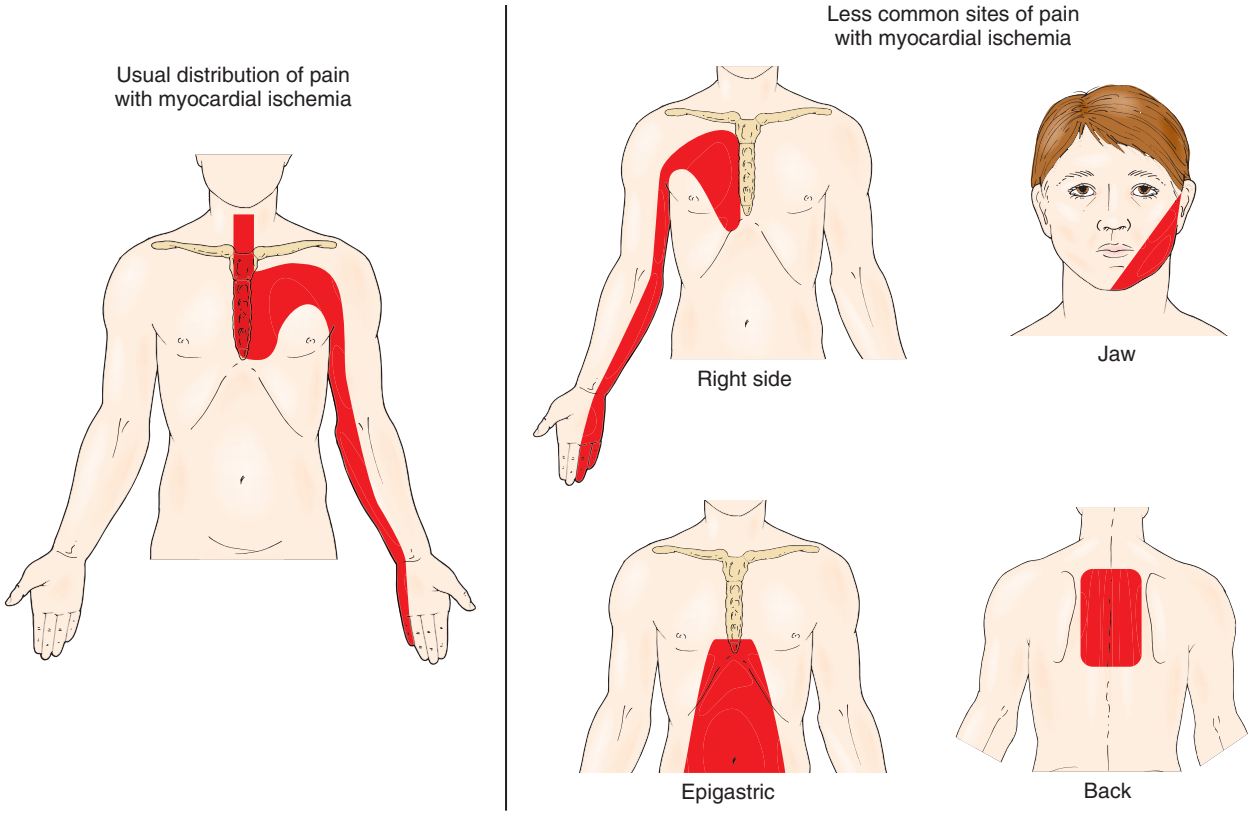

FIGURE 11–2 Pain patterns with myocardial ischemia. The usual distribution is referral to all or part of the sternal region, the left side of the chest, and the neck and down the ulnar side of the left forearm and hand. With severe ischemic pain, the right chest and right arm are often involved as well, although isolated involvement of these areas is rare. Other sites sometimes involved, either alone or together with other sites, are the jaw, epigastrium, and back. *(From Braunwald E: The history. In Braunwald E, Zipes DP, Libby P [eds]: Heart Disease, 6th ed. Philadelphia, Saunders, 2001, p 33.)*

The electrocardiogram and biochemical markers of myocardial necrosis (discussed in other chapters) are very helpful both in diagnosis and risk stratification and, together with the clinical findings, are helpful in selecting therapy.

Other Diagnostic Modalities

Occasionally, the diagnosis of an acute coronary syndrome remains uncertain, despite the assessment of the history, physical examination, ECG, and cardiac markers. In these unusual circumstances, other diagnostic modalities may be used. In the setting of an acute coronary syndrome, the region of the myocardium that is ischemic becomes dysfunctional. If the dysfunctional region is large enough, a wall motion abnormality may be detected by two-dimensional echocardiography or magnetic resonance imaging (MRI). Myocardial perfusion can be evaluated using nuclear cardiac imaging techniques, MRI, and positron emission tomography (PET) scanning. The *absence* of a perfusion abnormality makes the diagnosis of acute ischemia unlikely. Finally, in patients in whom reperfusion therapy is being considered but the diagnosis remains uncertain, emergency coronary angiography can identify an occluded or severely stenotic coronary artery and allow for immediate percutaneous coronary intervention.

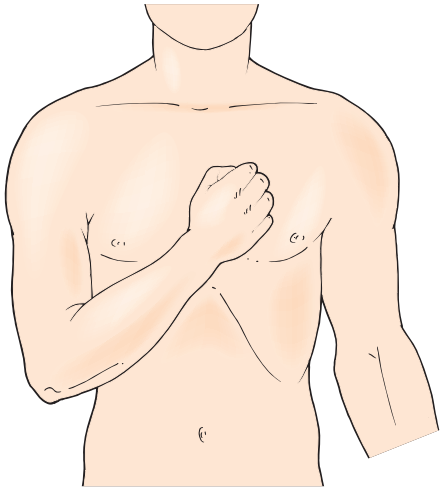

FIGURE 11–3 The Levine sign of acute myocardial ischemia. The clenched fist approximates the area of ischemic discomfort.

CLINICAL RECOGNITION OF ACUTE CORONARY SYNDROMES

Clinical recognition of acute coronary syndromes requires a careful history, physical examination, electrocardiography, and measurement of serum markers of myocardial injury and their integration, as noted. Timely and accurate clinical recognition is essential. Often, the repetition of certain aspects of the evaluation, such as the physical examination, ECG, and troponin level, can reveal previously undetected abnormalities that can aid in the diagnosis. This information should be

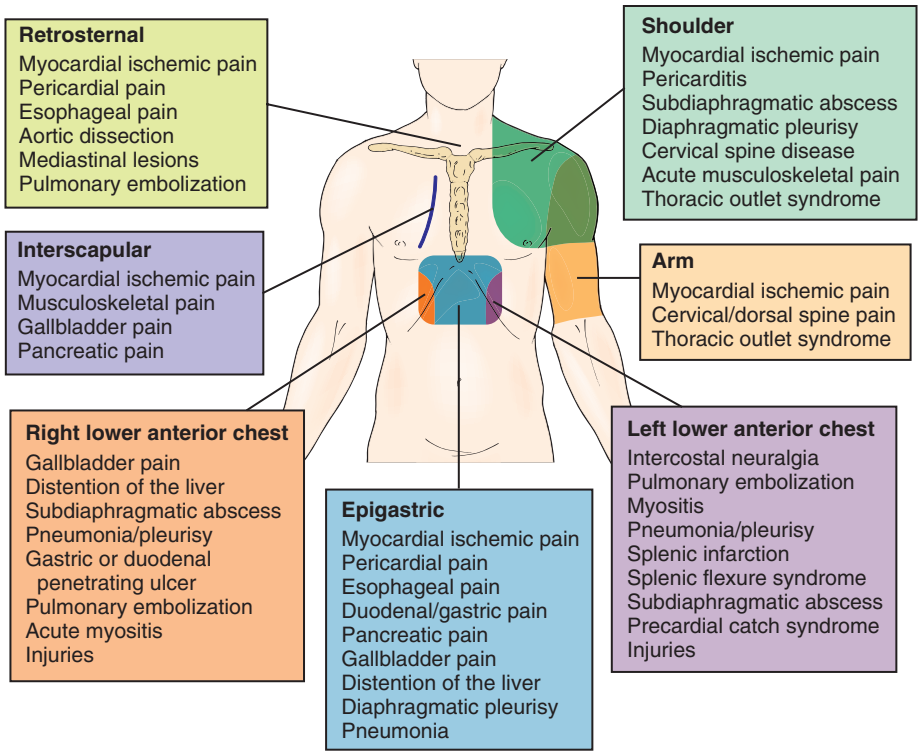

FIGURE 11–4 Differential diagnosis of chest pain according to where pain starts. Serious intrathoracic or subdiaphragmatic diseases are usually associated with pains that begin in the left anterior chest, left shoulder or upper arm, interscapular region, or epigastrium. *(From Braunwald E: The history. In Zipes DP, Libby P, Bonow RO, Braunwald E [eds]: Heart Disease, 7th ed. Philadelphia, Saunders, 2005, p 68.)*

used to establish the likelihood of the diagnosis of an acute coronary syndrome (Table 11-4) and the short-term risk of the development of an adverse outcome (Table 11-5). Rapid and appropriate treatment of this potentially life-threatening condition can then be initiated.

Acknowledgment

Dr. Howard A. Cooper was a coauthor of this chapter in the first edition of this book. Some of the material of that chapter has been carried forward into this edition. Dr. Cooper's efforts are gratefully acknowledged.

TABLE 11–4 Likelihood That Signs and Symptoms Represent an Acute Coronary Syndrome

Feature	Likelihood		
	High *(Any of the Following)*	**Intermediate** *(Absence of High-Likelihood Features and Presence of Any of the Following)*	**Low** *(Absence of High- or Intermediate-Likelihood Features but May Have the Following)*
History	Chest or left arm pain or discomfort as chief symptom	Chest or left arm pain or discomfort as chief symptoms	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics
	Known history of CAD, including MI	Age older than 70 yr, male gender	Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (1 mm or more) or T-wave inversion in multiple precordial leads	Fixed Q waves; ST depression 0.5 to 1 mm or T-wave inversion more than 1 mm	T-wave flattening or inversion less than 1 mm in leads with dominant R waves; normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB levels	Normal	Normal

CAD, coronary artery disease; CK-MB, MB isoenzyme of creatine kinase; MR, mitral regurgitation; TnI, troponin I; TnT, troponin T.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol 2007;50:e1-e157.

TABLE 11–5 Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients With Unstable Angina and Non–ST-Elevation Myocardial Infarction*

	Risk		
Feature	**High** ***(At Least one of the Following Features Must Be Present)***	**Intermediate** ***(No High-Risk Feature, but Must Have One of the Following)***	**Low** ***(No High- or Intermediate-Risk Features but May Have Any of the Following)***
History	Accelerating tempo of ischemic symptoms in preceding 48 hr	Prior MI, peripheral or cerebrovascular disease or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (longer than 20 min) rest pain	Prolonged (longer than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD; rest angina (longer than 20 min) or relieved with rest or sublingual NG; nocturnal angina; new-onset or progressive CCS class III or IV angina in the past 2 wk without prolonged (longer than 20 min) rest pain but with intermediate or high likelihood of CAD	Increased angina frequency, severity, or duration; angina provoked at a lower threshold; new-onset angina with onset 2 wk to 2 mo prior to presentation
Clinical findings	Pulmonary edema, most likely caused by ischemia; new or worsening MR murmur; S_3 or new or worsening rales; hypotension, bradycardia, tachycardia; age > 75 yr	Age > 70 yr	
ECG	Angina at rest with transient ST-segment changes > 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathologic Q waves or resting ST depression less than 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal
Cardiac markers	Elevated TnT, TnI, or CK-MB level (e.g., TnT or TnI > 0.1 ng/mL)	Slightly elevated cardiac TnT, TnI, or CK-MB level (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

*Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms.

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CK-MB, creatine kinase, MB fraction; MR, mitral regurgitation; NG, nitroglycerin; TnI, troponin I; TnT, troponin T.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol 50:e1-e157, 2007.

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CHAPTER 12

Biomarkers in Acute Ischemic Heart Disease

Joseph S. Alpert, Allan S. Jaffe, Kristian Thygesen, and Harvey D. White

In medicine, as in all human communication, it is essential to define the entities being discussed clearly. The history of medicine is replete with examples of communication failure resulting from poor definition of a particular disease entity. In clinical practice, as well as in clinical science, a clear definition of the disease diagnosed or studied is the first step in achieving effective control of that illness. Accurate, clear, and easily interpreted definitions of a disease entity allow physicians to communicate with each other, study the disease, and ultimately explain to patients the implications of the specific condition from which the patient suffers. A clinical scientist's diagnostic criteria must be accurate and reproducible, so that similar patients with the disease being studied can be entered into clinical trials. Eventually, the results of clinical trials involving patients with clearly defined diagnoses can be generalized for the management of other patients who satisfy the same disease criteria. Results from one clinical trial can be compared with the results of others, as long as the same disease definition and criteria are used.

Given the worldwide importance of morbidity and mortality related to cardiovascular disease, considerable scientific effort has been placed on identifying tools for defining the various syndromes of acute ischemic heart disease accurately. Biomarkers are adjunctive tests used with clinical findings to aid the physician in making an accurate clinical diagnosis of a specific disease entity, as well as in predicting its prognosis. Various biomarkers have been used for decades in patients with acute ischemic heart disease; however, the advent of highly specific troponin assays has resulted in a substantially improved ability to identify patients with acute ischemic heart disease and to gauge the level of risk of morbidity and mortality associated with these syndromes. Other biomarkers have been used in the past to detect myocardial necrosis; however, their use has been markedly attenuated with the advent of routine troponin determinations in daily clinical practice and clinical investigation.

WHAT IS A BIOMARKER?

The term was introduced in 1989 to mean a measurable and quantifiable biologic parameter (e.g., a concentration of a specific biologic substance) obtained from an individual. Its concentration implies certain pathophysiologic consequences. A variety of such biomarkers have been identified in a vast array of diseases. Most often, biomarkers are measured from blood samples. However, biomarkers from other body fluids or tissues are also of clinical and research significance.

The goal of cardiovascular biomarker determination is to enable clinicians to manage patients with heart and vascular disease optimally by defining the presence of a specific pathophysiologic process and by obtaining prognostic information about the disease that is present. A biomarker is valuable only if it can be accurately and reproducibly determined in clinical chemistry laboratories worldwide. The biomarker determination must be made under standardized conditions and associated with a high degree of sensitivity and specificity. Finally, the determination of specific biomarker levels must contribute to the overall management of the patient with the disease entity under evaluation if they are to be deemed cost-effective. Meticulous laboratory techniques must be used in collecting, processing, and measuring biomarkers if the values obtained are to be accurate and reproducible. Inadequate attention paid to the accuracy and reproducibility of the biomarker used can and will lead to confusion in the clinical setting, with possible associated medical error.

Biomarkers imply a variety of features about an individual's state of health or disease. Thus, biomarkers are seen to be indicators of the presence or absence of a disease or disease trait.[1] The use of troponin blood assays to define various syndromes of acute ischemic heart disease has gained worldwide use. Specifically, in the appropriate clinical setting, an elevated blood troponin level is used today as the gold standard for identifying acute ischemic myocardial necrosis—that is, acute myocardial infarction (MI).

The clinical definition of acute MI was one of the earliest disease entities for which biomarker diagnostic support was sought. Unfortunately, and until recently, the ideal of a universally understood and applied definition involving biomarker determination did not exist for MI. Over many decades, different definitions of MI have been used and, consequently, confusion has existed about the exact definition of MI. In the arena of public health statistics, similar problems have existed with different studies using varying definitions of MI. Statistics based on hospital discharge diagnosis of MI are also often inaccurate because the definitions of MI used vary from one physician to another.

As recently as 40 years ago, the biomarkers used for the diagnosis of acute MI were nonspecific, and often the assays were not highly reproducible from one laboratory to another. This led to intense scientific efforts to develop a highly reproducible, sensitive, and specific biomarker to identify myocardial necrosis to create a clearly defined algorithm for the definition of MI in its acute phase.

More than 30 years ago, the World Health Organization (WHO) sought to define MI accurately.[2] The criteria used, however, were often nonspecific or open to important interpretation bias. Thus, a patient's clinical chest discomfort or an equivalent symptom, for example, sudden onset of unexplained dyspnea, might be interpreted differently by different observers. Similarly, a reading of the same electrocardiogram (ECG) might vary among different expert electrocardiographers. Early biomarkers were nonspecific and assays were not highly reproducible. Consequently, biomarker measurement was not an important component of the original WHO definition of acute MI.

In an attempt to improve the accuracy of the diagnosis of MI for clinicians, and to make it easier to compare results from various clinical trials, a multinational task force met in 1999 under the auspices of the European Society of Cardiology and the American College of Cardiology. The task force sought to develop a simple, clinically oriented, universal definition for MI that could be used in daily clinical practice and in clinical investigation. The task force was successful in creating this definition, which was published simultaneously in the *European Heart Journal* and the *Journal of the American College of Cardiology*.[3]

Central to this new definition of MI was the use of highly sensitive and specific biomarkers determined from serial blood samples. The particular biomarker that has gained almost universal use in the diagnosis of MI is troponin (Fig. 12-1). This biomarker enables clinicians and clinical scientists to identify even small quantities of necrotic myocardium in the clinical setting. Given specific clinical settings and associated findings, such as ischemic changes in the ECG, the report of the task force in 2000 set criteria for both acute and established MI.[3] Recently, the definition was revised, based on scientific advances that have occurred since 2000.[4]

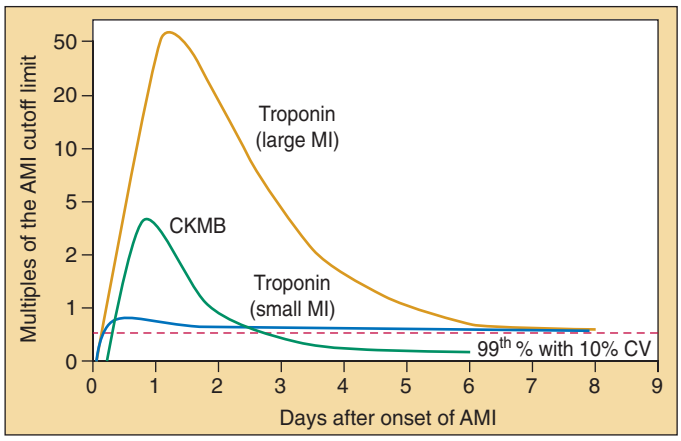

FIGURE 12–1 Time courses for elevation of various biomarkers after the onset of symptoms of acute myocardial infarction. Note the time course of the increase in troponin compared with CK-MB. With current assays and the use of the 99th percentile value, troponin values are seen to increase even earlier than myoglobin and CK isoforms.

The global definition of MI from the 2000 and 2007 reports[3,4] is based on troponin analysis and identify infarcts that may be too small to be seen with the naked eye during a routine pathologic examination. Biomarker diagnosis in patients with acute ischemic heart disease has become an essential component of the their diagnostic evaluation and care. The use of troponin level determinations in the routine management of patients with acute ischemic heart disease aids clinicians and clinical scientists more than merely making the diagnosis of myocardial necrosis more accurate. The presence and degree of elevation of blood troponin levels in a patient with an acute ischemic syndrome has important prognostic and therapeutic implications (see later).

Since the publication of the European Society of Cardiology (ESC)–American College of Cardiology (ACC) report in 2000, which emphasized the use of newer, highly sensitive and specific biomarkers of myocardial cell necrosis in the diagnosis of MI, many investigators have explored the implications of the revised definition of MI as compared with older, more traditional (and less specific) diagnostic criteria.[5-15] These studies have demonstrated that the modern troponin-based definition of MI has resulted in an increased number of patients identified as having had an MI. This finding is not surprising, because troponin is considerably more sensitive when compared with earlier biomarkers, such as creatine kinase MB (CK-MB). Because troponin identifies smaller infarcts than CK-MB, the acute or short-term prognosis for patients with troponin-positive, CK-MB–negative infarcts is better than that for patients with elevated troponin and CK-MB values.

This increase in the number of patients labeled with the disease entity, myocardial infarction, presents clinical and investigative cardiologists with a number of problems. For example, a patient who formerly would have been diagnosed as a case of angina pectoris or even unstable angina now falls under the diagnostic rubric of MI. The latter diagnosis carries important psychological and social implications for the patient. Depending on the patient's employment, certain careers may be interdicted by a diagnosis of MI and the specter of disability may be raised by the patient, family members, and/or employer. The personal and societal implications of the troponin-based definition of acute MI are discussed more fully later.

Given the importance of myocardial infarction seen from a clinical and societal perspective, the prospective investigation of Roger and colleagues[14] is of considerable scientific and clinical impact. These investigators used several standardized definitions of MI, including the one suggested by the first task force for the revision of the definition.[3] This comparison involved almost 2000 patients with the following discharge diagnoses—acute and old MI, unstable angina, coronary heart disease, angina pectoris, and other forms of ischemic heart disease. All patients had at least one, and often serial, determinations of blood troponin, creatine kinase (CK), and MB fraction of CK levels. The biochemical data were correlated with clinical information and short-term (30-day) outcome.

As expected, the new (troponin) definition of MI identified substantially more patients with ischemic myocardial necrosis than CK alone or CK combined with CK-MB. Depending on the level of troponin selected as the cutoff point beyond which MI was diagnosed, as well as on the number of samples taken, the percentage increase in the number of infarcts diagnosed by troponin alone ranged from 35% to 112%. Equally interesting was a much smaller but noticeable group of

patients who were diagnosed as having had an MI by their elevated CK-MB level, despite having a normal troponin value. Clearly, this small but clinically important group of patients was falsely diagnosed by the CK-MB criterion as substantiated by their excellent prognosis, both in the study by Roger and associates[14] and in others. However, the prognosis of those patients with smaller infarctions diagnosed solely by abnormal troponin values was better at 30 days (5% mortality) as compared with patients with larger infarctions who had both elevated troponin and positive CK or CK-MB (11% mortality) levels. These observations underscore the fact that troponin analysis increases sensitivity and specificity of infarct diagnosis.

DIAGNOSTIC APPLICATION OF BIOMARKERS IN THE UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

There have been considerable advances in the diagnosis and management of myocardial infarction since the original redefinition document was published. Consequently, together with the World Heart Federation (WHF), the ESC, ACC, and American Heart Association (AHA) convened a global task force to update the 2000 consensus document.[3] As with the previous consensus committee, the global task force was composed of a number of working groups to refine as precisely as possible the original ESC-ACC criteria for the diagnosis of MI from various perspectives. With this goal in mind, the working groups were composed of experts in the fields of biomarkers, electrocardiography, imaging, interventional cardiology, clinical investigation, and global perspectives and implications. During several task force meetings, the recommendations of the working groups were co-coordinated, resulting in an updated consensus document.[4]

Myocardial infarction is defined by pathology as myocardial cell death caused by prolonged ischemia. In a clinical setting, these conditions are met if the following criteria are present:

1. Detection of increase and/or decrease of cardiac biomarker levels
2. At least one value above the 99th percentile of the upper reference limit (URL), together with evidence of myocardial ischemia, as recognized by at least one of the following:
   - Symptoms of ischemia
   - ECG changes of new ischemia or development of pathologic Q waves,
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality[4]

Cardiac troponins I and T are the preferred markers for the diagnosis of myocardial injury because the troponins have almost absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[16] An increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of the URL. Detection of an increase and/or fall of the measurements is essential for the diagnosis of acute myocardial infarction (AMI), and optimal precision at the 99th percentile URL for each assay should be defined as a coefficient of variation (CV) ≤10%.[17,18] If troponin assays are not available, the best alternative is the MB fraction of CK as measured by mass assay. As with troponin, an increased CK-MB mass value is defined as a measurement above the 99th percentile URL using gender-appropriate normal ranges.

The increased sensitivity and specificity of the troponin biomarker depend not only on measuring the presence of the troponin molecule, but also on the ability of the assay to provide the necessary information.[19] Some assays, including most of those developed for point of care use, are not nearly as sensitive as those performed on the larger pieces of equipment used in central laboratories. One needs to be cautious in using point of care assays to avoid underidentification of patients at risk. There are also other problems that must be considered. Fibrin interference can occur and cause an occasional high troponin value.[20] If a value appears to be out of proportion to other values, it is suggested that the sample be respun and reassayed, especially if serum samples are being used. Uncommonly, there can be cross-reacting antibodies or antibodies to the proteins used to make the antibodies for troponin detection.[21,22] In general, this artifact is easy to detect. It should be suspected when values are elevated and stay reasonably constant over time.

As troponin assays have become more sensitive, it has become increasingly clear that a changing pattern of values is the key to distinguishing acute problems from more chronic ones. The ability to detect changes is heavily dependent on the precision of the assay. In general, there has been an advocacy for a 10% coefficient of variability at the 99th percentile of a normal population.[4,18] This standard has rarely been met with current assays, in which variability is substantially higher. For a while, this led some to advocate the use of a cutoff value equivalent to the 10% CV value to protect against false-positive results caused by imprecision.[23] This turns out to be unnecessary because it is now clear that true normal values are far lower than those that can be measured with contemporary assays.[24] However, assay imprecision makes it much more difficult to detect when a true increase occurs. Thus, assays that are very imprecise will require very large values to show differences, whereas those that are more precise will require lower values.[25] Usually, once values are significantly elevated, all assays yield fairly good results, with relatively low levels of imprecision. In that situation, a 20% change, or roughly an approximately 5% to 7% CV, can be assumed.[26]

If one uses sensitive assays and the 99th percentile URL, the troponin level will be seen to increase more rapidly than the CK-MB level (see Fig. 12-1); the use of biomarkers such as myoglobin and other putatively rapidly increasing markers is thus no longer necessary to establish the diagnosis of AMI.[27-29] This value also maximizes the sensitivity and specificity of troponin values in patients with MI (Fig. 12-2).[30] In addition, the diagnosis of AMI can be made in as many as 80% of patients within 3 hours of presentation, even if one selects a cohort that presents early (all within 4 hours) to evaluate.[31] Late detection is also facilitated.[32] This is because the rate of increase of the troponin level allows one to detect these values at an earlier point in time. The use of the rate of increase and the association with the 99th percentile URL facilitates the rapidity and accuracy of diagnosis.

Both cardiac troponin I (cTnI) and cardiac troponin T (cTnT), assuming good assays and appropriate cutoff values, perform comparably in terms of their diagnostic proficiency. The one difference occurs in renal failure patients, in whom there are many more elevations of cTnT than cTnI levels.[33] Pathologic studies have suggested that these elevations denote cardiac abnormalities and are highly prognostic.[34-38] Thus, patients who have elevated levels of cTnT require evaluation, but they may not have acute myocardial disease. When these patients present with MI, their subsequent cTn values increase from the elevated baseline. A rising pattern of cTn values distinguishes those who have acute disease from those with chronic elevations. Patients with troponin level elevations and MI are a particularly high-risk group.

The prognostic significance of troponin seems to exist across heterogeneous clinical situations.[18] Once the diagnosis of acute coronary syndrome is confirmed, the prognostic significance of an elevated troponin level is clear. In patients

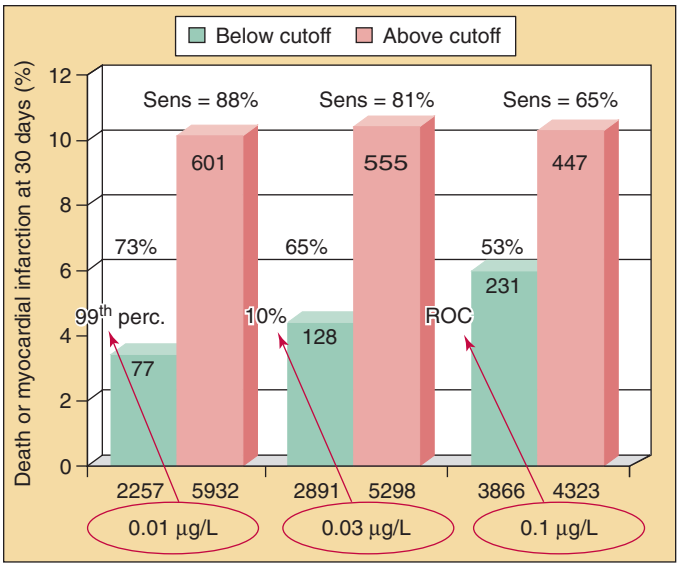

FIGURE 12–2 Various cutoff values used in the GUSTO IV MI trial. Note the improved specificity and sensitivity of the 99th percentile value. *(From James S, Armstrong P, Califf R, et al: Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: Prospective verification in the GUSTO-IV trial. Am J Med 2003;115:178-184.)*

who have ST-segment elevation MI (STEMI), those with elevated troponin levels are at increased risk for subsequent adverse events.[39,40] This is partially related to the fact that it takes time for the troponin level to increase. However, when analyses have been done attempting to correct for the time from the onset of symptoms to presentation, the effect is still noted. In studies with primary angioplasty, the procedural success rate is lower if the troponin level is elevated at the time of presentation than if it is not.[41] With non-STEMI (NSTEMI), the finding of an elevated troponin level presages an adverse short-term outcome and usually indicates the need for aggressive anticoagulant therapy and early interventional therapy.[42-52] However, there can be a heterogeneity of causes for myocardial infarction (Table 12-1). MI can be a spontaneous event related to plaque rupture or fissuring, dissection of an atherosclerotic plaque or, as recently described, nodular plaque rupture, a type 1 MI.[4] Alternatively, MI can be caused by increased myocardial oxygen demand when the ability of the heart to increase coronary supply is incommensurate with that demand. This could be the result of anemia, arrhythmia, hypertension or hypotension, vasoconstriction, or arterial spasm causing a marked reduction in the degree of myocardial blood flow, known as a type 2 MI. In addition, elevations of troponin levels associated with percutaneous coronary intervention (PCI; type 4a MI) should also be designated AMI because they are caused by ischemia. Another subtype of type 4 MI is type 4b, which is the result of stent thrombosis. Finally, elevations of troponin levels can be used to assist in the diagnosis of a type 5 MI (i.e., an infarct associated with coronary artery bypass grafting [CABG]). The one circumstance in which biomarkers are not of value is when the patient with a typical presentation for myocardial ischemia or MI dies before it is possible to detect blood biomarker elevation, either because the test sample was not obtained or measured before the patient succumbed. Such patients are designated as having a type 3 MI.

TABLE 12–1 Classification of Myocardial Infarction

Type	Features
1	Spontaneous myocardial infarction related to ischemia caused by a primary coronary event (e.g., plaque erosion or rupture, fissuring, dissection)
2	Myocardial infarction secondary to ischemia caused by imbalance between oxygen demand and supply (e.g., coronary spasm, anemia, hypotension)
3	Sudden cardiac death, with symptoms of ischemia, accompanied by new ST elevation or left bundle branch block, or verified coronary thrombus by angiography or autopsy, but death occurring before blood samples could be obtained
4a	MI associated with PCI
4b	MI associated with verified stent thrombosis
5	MI associated with CABG

Adapted from Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-2538.

Once elevations of biomarkers are present, as in these patients, attempting to differentiate the effects of the NSTEMI on the troponin levels from those associated with the PCI itself is impossible, which is why a normal baseline value is essential if a diagnosis of post-PCI AMI is to be made.[4] The prognostic significance of an elevated troponin value is related to the magnitude of the elevation. As smaller and smaller degrees of cardiac injury can be detected, prognosis of those patients with lower values is slightly less adverse than in those who present with higher values.[14] Troponin measurement is also helpful in the management of patients with acute coronary syndromes and in the post-PCI setting, as noted, as well as in the diagnosis of reinfarction when patients have recurrent chest discomfort. Recent data have suggested that the troponin measurement is as accurate as the determination of CK-MB for identifying reinfarction (Fig. 12-3).[53,54] Given the increased sensitivity and specificity of troponin, one would suspect that if a trial were performed comparing troponin with CK-MB for the identification of reinfarction, the former biomarker would actually be superior (see Fig. 12-3).

Effect of the New Troponin-Based Definition of Myocardial Infarction

The ESC and ACC redefined the criteria for the diagnosis of MI in 2000.[3,4] The diagnosis was changed from one based on epidemiology to a definition based on elevation of the troponin level in the clinical setting of myocardial ischemia. This change dramatically increased the frequency of the diagnosis of MI and affected epidemiologic studies and clinical practice, with the prognosis for MI being improved. Employment, health insurance, and evaluation of health care delivery have also been affected.

In a small study of 401 patients admitted with suspected cardiac chest pain, implementation of the redefinition criteria increased the numbers of patients with an MI by 26.1% as compared with the WHO classification.[6] It is notable that the WHO criteria resulted in false-positive rates of MI diagnosis of approximately 5%.[7] Most of the additional patients with the diagnosis of MI were previously diagnosed as having unstable angina but 33% were previously diagnosed as having other cardiac or noncardiac diagnoses.

In a prospective U.S. community study of 1851 patients presenting with cardiac pain, the use of contemporary cut points for troponin T assays (with an increase or decrease >0.03 µg/mL for the diagnosis of MI), there was a 74% increase over CK and a 41% increase over CK-MB criteria for MI.[20] If a criterion of an increase in only one troponin level was used, the increase in diagnosis over the CK criterion was 112%. The increase was particularly robust in women.

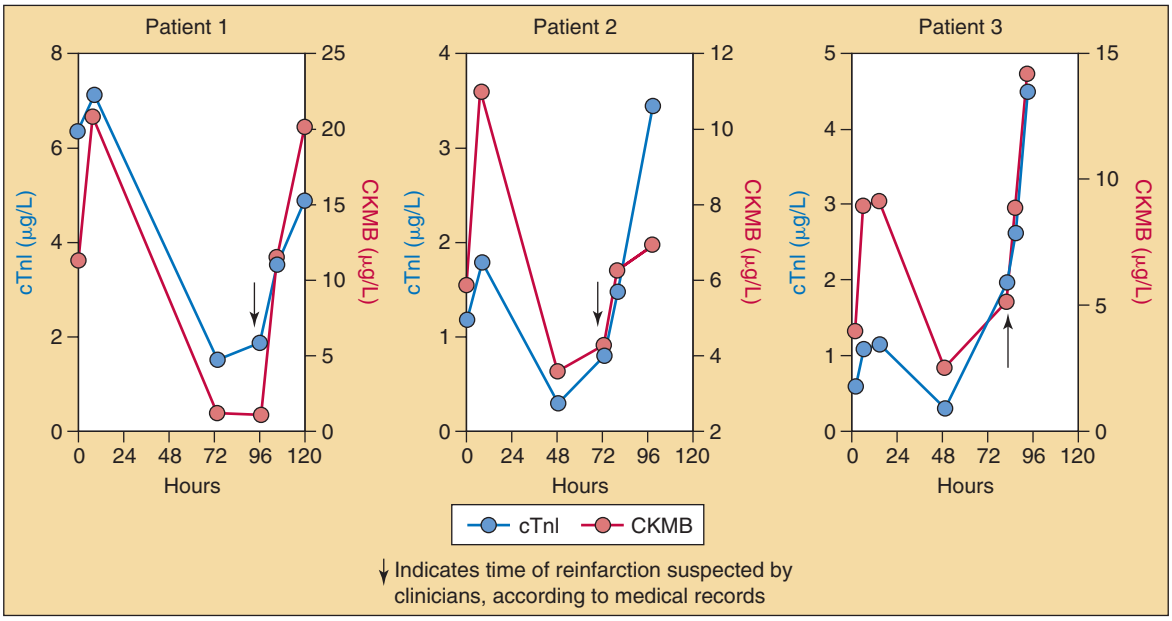

FIGURE 12–3 Use of CK-MB and cTnI for detection of reinfarction after myocardial infarction. *(From Apple F, Murakami M: Cardiac troponin and creatine kinase MB monitoring during in-hospital myocardial reinfarction. Clin Chem 2005;51:460-463.)*

Patients diagnosed with troponin-only criteria were at increased risk but at less risk than those who also had elevated CK-MB levels.[14]

General Implications of Redefining Myocardial Infarction

Evolution of the definition of a specific diagnosis such as AMI has a number of implications for individuals, as well as for society at large. The process of assigning a specific diagnosis to a patient should be associated with a specific value for that patient. The resources spent on recording and tracking a particular diagnosis must also have a specific value to society to justify the effort. A tentative or final diagnosis is the basis for advice about further diagnostic testing, treatment, lifestyle changes, and prognosis for the patient. The aggregate of patients with a particular diagnosis is the basis for health care planning and policy and resource allocation.

One of the goals of good clinical practice is to reach a definitive and specific diagnosis, supported by current scientific knowledge. The currently revised approach to the definition of MI meets this goal. Thus, the current diagnosis of AMI is a clinical diagnosis based on patient symptoms, ECG changes, and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques. However, it is important to characterize the extent of the infarct, residual left ventricular function, and severity of associated coronary artery disease, as opposed merely to diagnosing MI. The information conveyed about the patient's prognosis and ability to return to work requires more than just the statement that the patient has suffered an infarct. The other factors noted are also required so that appropriate social, family, and employment decisions can be made. A number of risk scores have been developed for predicting postinfarction prognosis. The classification of the various other prognostic entities associated with myocardial necrosis should lead to a reconsideration of the clinical coding entities currently used for patients with the myriad conditions that can lead to myocardial necrosis, with consequent elevation of biomarker levels.

The change in the definition of MI will have a substantial impact on the identification, prevention, and treatment of cardiovascular disease globally. The new definition will affect epidemiologic data from developing countries relating to prevalence and incidence. Cultural, financial, structural, and organizational problems relating to diagnosis and therapy of AMI will require ongoing investigation. It is essential that the gap between therapeutic and diagnostic advances be addressed in this expanding area of cardiovascular disease.

Case Studies of Correct Interpretation of Blood Troponin Results

The high sensitivity and specificity of abnormal blood troponin levels for the detection of myocardial cell necrosis represents a potential aid and possible hazard for the clinician. On the one hand, this highly sensitive biomarker can be used to demonstrate that a patient has suffered a small but potentially dangerous MI. This information should lead the clinician to follow an aggressive medical and often concomitant interventional therapeutic strategy. On the other hand, an elevated troponin level in a patient with multisystem disease involving pathologic states such as respiratory and renal failure usually signifies collateral myocardial necrosis secondary to the underlying medical conditions. The latter situation is not an ischemic MI and should not be treated as such. The section of this chapter dealing with troponin measurement and its implications has listed a number of clinical entities in addition to MI that could lead to abnormally elevated blood troponin levels. When elevated troponin levels are found in such patients, this invariably implies a worsened prognosis for the patient, even though an ischemic myocardial infarction has not occurred. The following three case studies will demonstrate the points just made.

Case 1

A 60-year-old man awakens in the early morning hours with a progressively severe episode of central chest discomfort.

The patient has had stable angina pectoris for several years, treated medically. His physician has informed him about symptoms that might occur with an AMI and the patient dissolves first one and then a second nitroglycerin tablet beneath his tongue. The discomfort gradually fades after approximately 1 hour. His wife is awakened by her husband's restlessness and insists that they drive immediately to the emergency department. On arrival at the hospital, an ECG demonstrates 1.5 mm of new ST-segment depression in leads V3 to V6. A blood troponin level obtained on admission to the emergency department is elevated. The patient is treated with additional aspirin, clopidogrel, low-molecular-weight heparin, and intravenous beta blockade. His discomfort has now completely resolved, and he is admitted to the hospital where later that morning he undergoes a cardiac catheterization. This demonstrates an ulcerated plaque with overlying thrombus almost totally occluding the mid–left anterior descending artery. The patient has this lesion treated with a stent. The patient is then started on an intravenous glycoprotein (GP) IIb/IIIa inhibitor in the catheterization laboratory, and later in the day statin and angiotensin-converting enzyme inhibitor therapy is initiated following the interventional cardiac procedure. His recovery is uneventful. A subsequent transthoracic echocardiogram a month later demonstrates mild to moderate hypokinesis of the anterior wall of the left ventricle.

COMMENT: This patient's clinical scenario (symptoms and ECG abnormalities), taken together with an elevated blood troponin level, demonstrate that an AMI of the non–ST-segment elevation variety had occurred because of plaque rupture. This would be a type 1 AMI. The patient was managed appropriately with modern, evidence-based, medical and interventional therapy. His recovery was aided by establishing the correct diagnosis with the assistance of blood troponin measurement.

Case 2

A 50-year-old woman with chronic renal failure secondary to interstitial nephritis treated with chronic dialysis develops extensive bronchopneumonia. She is brought to the emergency department by her family, where hypoxemia and hypotension are documented. She is markedly tachypneic and requires intubation shortly after arriving in the emergency room. She is admitted to the medical intensive care unit (MICU) and has a stormy 3-week course there, which includes sepsis, delirium, and adult respiratory distress syndrome, complicated by recurrent bouts of severe hypoxemia and hypotension. Repeated ECGs demonstrate only modest nonspecific ST-T wave changes that are not noted to be labile. Several times during her protracted MICU admission, elevated blood troponin values are demonstrated. A transthoracic echocardiogram demonstrates mild, diffuse left ventricular dysfunction, with a global left ventricular ejection fraction of 48%. The patient is treated with assisted ventilation, frequent dialysis, intravenous antibiotics, and intravenous pressors. She gradually recovers. She does not undergo cardiac catheterization during her admission. Two months later, a repeat transthoracic echocardiogram demonstrates normal left ventricular function, with a global ejection fraction of 67%.

COMMENT: This patient had myocyte necrosis as a result of severe multisystem illness. The myocardial injury was correctly presumed to be the result of a combination of factors, including hypoxemia, hypotension, and markedly elevated blood values of various inflammatory cytokines. All these factors led to her modest myocardial injury. At no time during her hospitalization did her ECG or clinical course suggest acute ischemia. It is possible, however, that if atherosclerotic disease were present in this patient, that some of the myocyte necrosis detected by troponin could have been caused by myocardial ischemia secondary to presumably fixed atherosclerotic coronary artery disease. Her subsequently normal echocardiogram supports the diagnosis, made in the MICU, of myocyte necrosis secondary to the patient's severe multisystem illness. Her myocardial injury subsequently resolved and her left ventricular ejection fraction normalized following her recovery.

Case 3

A 35-year-old man with known familial dilated cardiomyopathy and moderately symptomatic (New York Heart Association [NYHA] Class II) chronic congestive heart failure is managed as an outpatient with an extensive oral medical regimen consisting of carvedilol, lisinopril, furosemide, spironolactone, digoxin, aspirin, and isosorbide mononitrate. He is followed closely by his internist and cardiologist. He participates in a supervised cardiac rehabilitation exercise program, which includes a component of moderate weight training. On a routine office visit to the internist, the patient complains of right chest discomfort the day after upper extremity weight exercises. On physical examination, the physician notes moderate right pectoral muscle tenderness. Blood troponin and brain natriuretic peptide (BNP) levels are ordered. The results for both blood biomarkers are moderately elevated. The BNP value has been elevated in the past, but this is the first time that a troponin level has been measured. The patient does not have a family history of atherosclerotic heart disease or diabetes mellitus and his systolic blood pressure readings measured in the physician's office and at home have always been below 110 mm Hg. A recent lipid panel was normal, with total cholesterol of 145 mg/dL and a low-density lipoprotein (LDL) cholesterol value of 68 mg/dL. His physicians discuss the laboratory and clinical findings and decide that the elevated troponin level is caused by his dilated cardiomyopathy and not by ischemic heart disease. The dosages of his medications are increased serially over several weeks. His BNP level returns to normal with increased medical therapy, but troponin levels remain mildly and persistently elevated. His chest discomfort resolves with local heat and rest. He reports that his effort dyspnea is improved with the increased intensity of medical therapy.

COMMENT: This patient's elevated troponin value denotes ongoing myocyte necrosis secondary to his underlying familial dilated cardiomyopathy. It is possible that he has endothelial dysfunction or supply demand imbalance in the subendocardium and thus, in one sense, has some ischemic injury to his myocardium, but this is not the result of plaque rupture or atherosclerotic coronary heart disease. The elevated blood troponin value is not the result of atherosclerotic ischemic injury to his myocardium, and hence is not indicative of an acute AMI. However, a persistently elevated troponin level in a patient with chronic heart failure implies a poorer prognosis for this patient than would be the case if the blood troponin level had been normal.

These three scenarios are examples of elevated troponin blood levels in three patients with different causes for this abnormal laboratory result. In the first patient, the elevated troponin value together with supportive clinical information led to the diagnosis of AMI, with the institution of appropriate, evidence-based therapy. In the second case, the patient developed myocardial necrosis secondary to a life-threatening multisystem illness. This patient's myocardium recovered once the patient's severe illness resolved. In the third example, blood troponin levels were elevated secondary to a chronic pathologic process involving the patient's myocardium. Atherosclerotic ischemic heart disease with plaque rupture and coronary arterial thrombosis was not present in either of the latter two patients.

USE OF OTHER BIOMARKERS

Advances in vascular biology have led to the development of a plethora of biomarkers associated with various levels of risk following an acute coronary syndrome (MI). Many of these biomarkers have been shown to have independent prognostic significance but often the measurement of these new markers has been compared to less than optimally used troponin values. These include the prothrombotic inflammatory marker CD40,[55] adhesion molecules,[56] interleukin (IL),[57] matrix metalloproteinases,[58] and pancreatic phospholipase A2 (PPLA2), which is associated with plaque stability.[59] Higher levels of the anti-inflammatory marker interleukin-10 are associated with fewer ischemic events.[60] However, despite intriguing initial data using various new biomarkers, the only two leading candidates to be incorporated into clinical practice are C-reactive protein (CRP) and BNP.

Risk Assessment

Using C-Reactive Protein

CRP is the best studied of the inflammatory markers.[61-71] It is synthesized by the liver in response to the activation of IL-1 and IL-6 and tumor necrosis factor-α. CRP is increased with inflammation and is found in atheromatous plaques, perhaps contributing to plaque instability. Genetic variation in the CRP gene has been shown to be associated with CRP levels and risk of MI, stroke, and cardiovascular mortality.

High-sensitivity CRP has been shown in 22 prospective studies to be associated with an odds ratio of 1.45 for the risk of coronary heart disease in general healthy populations.[63] In MI, levels are related to inflammation in atherosclerotic plaques; the response to myocyte necrosis and ischemia alone does not increase levels.[64] In patients with myocyte necrosis, levels increase rapidly, doubling every 8 hours and peaking 2 to 4 days after the onset of ischemia.[65] Levels return to baseline by 2 to 4 weeks.

High-sensitivity (hs) CRP has been shown to be independently associated with short- and long-term patient risk in NSTEMI and in STEMI. In patients with unstable angina, patients with an hsCRP >3.0 mg/L had higher rates of in-hospital recurrent ischemia, death, MI, or revascularization than patients with lower levels.[66] In the TIMI IIA trial, patients with hsCRP levels >15.5 mg/L had 10 times the risk of death at 14 days compared with patients with lower levels of hsCRP.[67] In the CAPTURE trial, hsCRP levels >10 mg/L were independently associated with death and MI.[68] In the FRISC trial, patients with baseline hsCRP levels >10 mg/L had higher rates of cardiovascular death at 3 years, 16.5% versus 5.7% for patients with levels <2.0 mg/L.[69] In the GUSTO IV study, hsCRP levels >10 mg/L were correlated with higher 1-year mortality.[70]

In patients with STEMI, hsCRP levels >3 mg/L have been associated with increased risk of in-hospital recurrent ischemia or MI.[71] Levels >10 mg have been associated with death and MI at 30 days,[72] levels >20 mg/L with death at 1 year,[73] and levels >25 mg/L with death or MI or angina at 1 year.[70] Some studies with early sampling before CRP levels increase in response to myocyte necrosis have not shown a relationship of hsCRP levels to mortality.[74] Very high levels (>200 mg/L) have been associated with the risk of ventricular rupture.[73]

Discharge levels of hsCRP have been shown to be more predictive of 1-year rates of death, MI, and recurrent ischemia than admission levels.[75] In the CARE study, patients with hsCRP levels ≥10 mg/L measured 6 to 20 months after MI had an increased risk of coronary heart disease, death, or MI.[76] In the PROVE-IT study, early lipid lowering following MI levels of hsCRP <2.0 mg/L achieved with either atorvastatin or pravastatin were associated with lower rates of death or MI,[77] and hsCRP levels <1.0 mg/L were associated with even lower event rates.

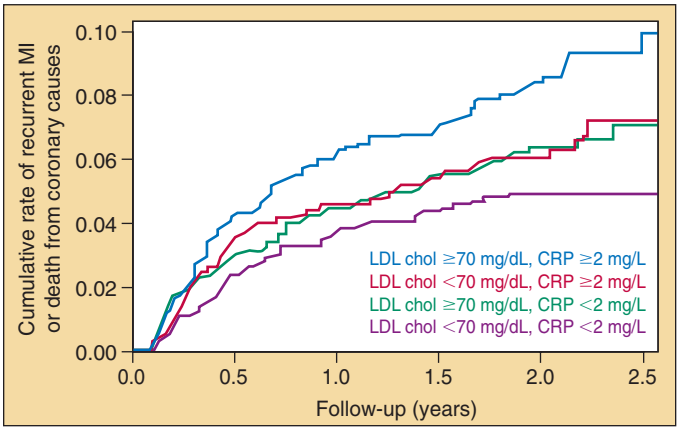

FIGURE 12–4 Prognostic effect of LDL and CRP measured post-MI. Note that both CRP and LDL had potent prognostic effects. *(From Ridker PM, Cannon CP, Morrow D, et al: C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20-28.)*

Recent data may help synthesize the value of CRP. Most results of the previous trials have suggested that CRP predicts later events than troponin. The recent PROVE-IT data may be helpful in understanding this finding (Fig. 12-4).[77,78] Values of CRP that remained elevated 4 to 6 weeks after MI identified patients with multiple risk factors (e.g., obesity, smoking, diabetes) who were at risk for subsequent events, even if LDL levels were controlled.

There are a number of issues related to the clinical use of hsCRP. First, levels change dramatically from presentation with MI to a later recovery period. Timing of measurement is thus important for the interpretation of hsCRP levels. The association of elevated CRP levels may be stronger with risk of mortality than with risk of MI.[60] The optimal cut point for risk stratification has not been defined nor has the target level if therapeutic approaches to lower CRP are used, such as aspirin,[79] statins,[80] or ezetimibe.[81]

Using B-Type Natriuretic Peptide

BNP and N-terminal (NT)–pro-BNP are produced in the ventricles and correlate with left ventricular pressure. Release is stimulated by a number of stimuli, including hypoxia, ischemia, increased wall stress, and dilation of the ventricles or atria.

Increase in the levels of these biomarkers with ischemia is caused by myocardial stretch.[82] BNP is synthesized as pro-BNP, which is made up of 108 amino acids. When released into the circulation, pro-BNP is cleaved into the C-terminal fragment, BNP, which is biologically active and made up of 32 amino acids, and the inactive N-terminal fragment, NT–pro-BNP, which is made up of 76 amino acids. The half-life of BNP is 20 minutes and of NT–pro-BNP is 120 minutes.

There are numerous BNP assays, and the results of different assays cannot be compared with each other or with NT–pro-BNP results. Both are powerful predictors of death and MI in NSTEMI, independently of markers of myocardial necrosis (e.g., troponin) and markers of inflammation (e.g., CRP).[83-89] However, in most studies, the prognostic significance is predominantly in those patients with normal troponin values when contemporary assays and recommended cutoff values are used. They have not been predictive of recurrent ischemia. Similar findings have been reported in STEMI.

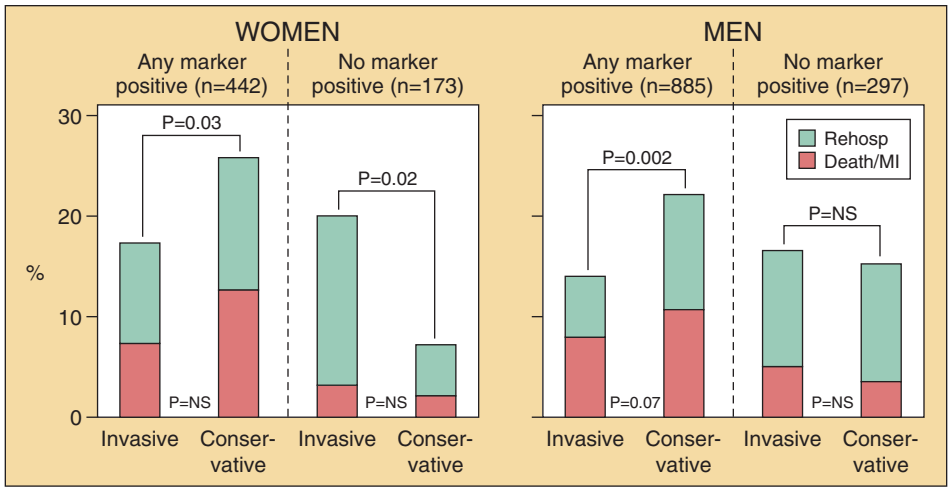

FIGURE 12–5 Outcomes by gender in the Tactics TIMI 18 trial. Note that women most often had elevated values of CRP and/or BNP rather than of troponin. Men tended to have many more elevations in troponin. *(From Bodi V, Sanchis J, Llacer A, et al: Multimarker risk strategy for predicting 1-month and 1-year major events in non–ST-elevation acute coronary syndromes. Am Heart J 2005;149:268-274.)*

There has been conflicting evidence concerning the value of BNP for predicting the benefit of revascularization.[86,90,91] In the TACTICS-TIMI-18 trial, elevated BNP levels were not associated with a benefit of revascularization,[86] except in women (Fig. 12-5). In the FRISC-II study, however, there was a trend for patients with NT–pro-BNP levels in the highest tertile to benefit from revascularization.[92] There was a significant benefit of revascularization in patients who had elevated NT–pro-BNP levels and elevated levels of an inflammatory marker, IL-6. In both trials, BNP and NT–pro-BNP, respectively, were related to the existence of angiographic coronary disease but not to recurrent ischemic events.

Dynamic risk assessment with changes in BNP over time may lead to better prediction of risk. In the PRISM study, levels at 72 hours added additional prognostic value to those taken at admission.[92] Increases in NT–pro-BNP following admission were associated with higher rates of death and MI. Conversely, rapid decline in NT–pro-BNP levels were associated with low event rates. The combination of normal troponin levels and low BNP levels was associated with a very low risk of ischemic events.

There are a number of issues to be resolved before BNP can be recommended for routine clinical use in acute coronary syndromes. The optimal time to test for BNP and NT–pro-BNP has not been defined. In one study, there was no difference in the predictive value for samples taken on admission as compared with those taken at 72 hours.[93] In the PRISM study, however, levels at 72 hours added additional prognostic value to those taken at admission.[92] In the FRISC II study, levels measured at 3 and 6 months had better predictive value than levels measured at admission or at 48 hours.[88] At this time, definitive cutoff levels for prognostic prediction have not been clearly defined.

Multimarker Risk Stratification

The combination of risk factors related to differing pathophysiology for risk assessment may lead to better risk prediction. Thus, combining markers of myocyte necrosis (e.g., troponins) with markers of inflammation (e.g., hsCRP) and markers of myocardial ischemia (e.g., BNP related to myocardial stretch) is attractive. This approach has been tested in several studies and has been shown to provide a more comprehensive risk assessment[86,94-96] and add to clinical risk assessment by the TIMI risk score.[97]

POTENTIAL IMPROVEMENTS IN BIOMARKER ANALYSES IN THE FUTURE

Advances in techniques and uses for biomarkers will undoubtedly occur in the future. The techniques that are probably most advanced at present are more sensitive assays for cardiac troponin. There is substantial evidence that there is additional prognostic and pathophysiologic information in values below the presently measured 99th percentile URL value.[24,25,97-99] It appears that normal values, if detectable at all, are 10 to 20 times lower than what is being measured currently. If so, more sensitive assays will markedly improve the ability to identify individuals with acute ischemic heart disease,[100] but there will be a price to pay for this increased sensitivity.

New data, including follow-up studies, show that values of cTnI that are 50% reduced from the 99th percentile are associated with more cardiovascular events over time in those with and without known heart disease,[97] as well as in patients presenting with chest pain and MI (Figs. 12-6 and 12-7).[98] During long-term follow-up, such elevations in troponin values have prognostic significance.[99] Thus, lowering the cutoff value indicative of myocardial necrosis still further is clearly important as assays become more sensitive. However, there is also evidence, based on current assays, that demonstrates elevations in cTn in the absence of acute disease.[33-38,93,100-102] This has been best appreciated in patients with severe renal dysfunction although it also is seen in patients with other conditions.[104] In the Dallas Heart study,[102] 0.7% of the general population had values of cTnT above the 99th percentile. They usually had heart failure, renal failure, left ventricular hypertrophy (LVH), and diabetes, and frequently all four. Troponin elevations were modest but the cTnT assay used was not the most sensitive technique available, so these values might even be higher with more sensitive assays.

This means that with more sensitive assays, it may be difficult to distinguish acute disease processes from those that are more chronic. This latter point appears to be the case for patients with renal failure,[36] and it is likely to be same for patients with chronic elevations as a result of different disorders. The more sensitive troponin assays still require more validation before they can be used clinically. At times, claims for a more sensitive assay may merely represent a marked change from a previously insensitive test. Nevertheless, even the increased sensitivity of the newer generation of troponin

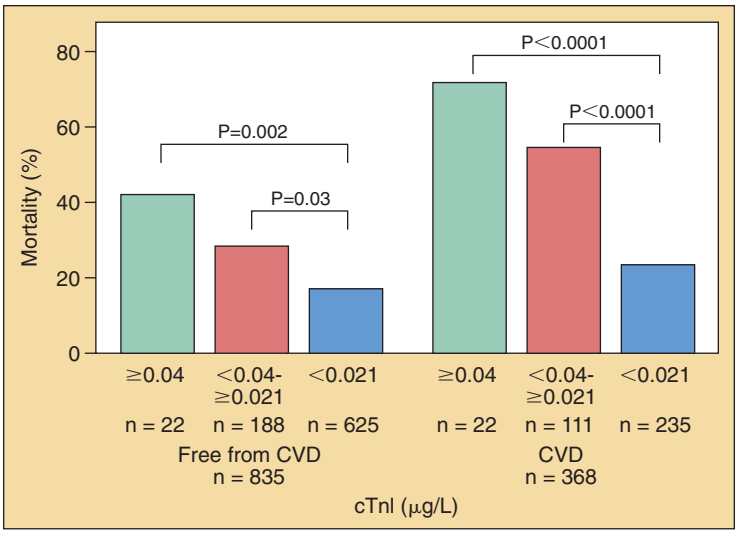

FIGURE 12–6 Patients with troponin values lower than the 99th percentile value of 0.04 μg/L but higher than 0.02 μg/L. The limit of detection of the assay had more cardiac events over time than those with undetectable values. CVD, cardiovascular disease. *(From Zethelius B, Johnston NP: Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: A community-based cohort study. Circulation 2006;113:1071-1078.)*

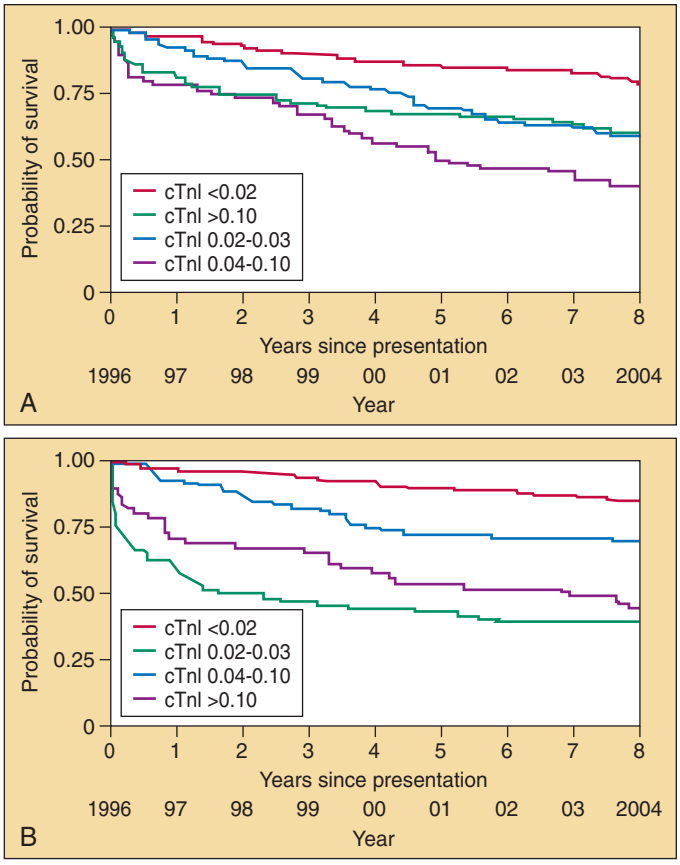

FIGURE 12–7 Individuals with values between 0.02 and 0.04 ng/mL, which are below the putative 99th percentile for this assay, had more events over time after presenting with possible MI compared with those with undetectable values. **A,** Mortality. **B,** MI and congestive heart failure. *(From Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-2538.)*

assays should be helpful to the clinician. For example, using these assays, true-positive results are detected far earlier than with insensitive assays, and there is evidence to suggest that 80% of patients with MI can be diagnosed within 3 hours using this approach.[25,31,99,103] Therefore, techniques measuring myoglobin and CK isoform levels no longer provide additional early information. With still more sensitive troponin assays, all these trends are likely to continue. Hence, any newly developed markers will need to compete not only with current troponin assays, but with those still more sensitive methods that are being developed.

The newer troponin assays will have to compete with new markers said to improve early detection and/or prognosis in patients with MI.[104,105] Most of these approaches focus on measuring molecules related to ongoing events in the so-called vulnerable plaque. It may be possible to monitor the biochemistry of such plaques and predict or confirm a plaque rupture event. A large number of reports in this area using biomarkers such as myeloperoxidase, soluble CD40 ligand, placental growth factor, and pregnancy-associated plasma protein A (PAPP-A) have not used contemporary assays for cTn and/or appropriate cutoff values in the initial validation of these markers.[106] Continuing investigation will clarify the role of these new biomarkers compared with high-sensitivity troponin assays.

It is clear that patients with MI, particularly NSTEMI, are not a homogeneous group. As many as 10% to 15% of these patients, for example, have normal coronary arteries, despite a classic initial presentation (Fig. 12-8).[107] If these individuals have elevated cTn values, they appear to do worse. Recent data suggest that many of these patients, especially women, with normal coronary arteries have evidence of what appears to be myocardial infarction by magnetic resonance imaging (MRI).[106] The pathophysiology of this entity is unclear. It could be related to endothelial dysfunction or dissolution of thrombus prior to angiography. A marker of heightened coagulation associated with NSTEMI might be valuable for identifying individuals with a propensity for atherothrombosis. The absence of elevation in a marker for plaque rupture or endothelial dysfunction might help distinguish this group. There are a large number of candidate biomarkers for each of these situations. Such markers might also improve the ability to identify women with NSTEMI.

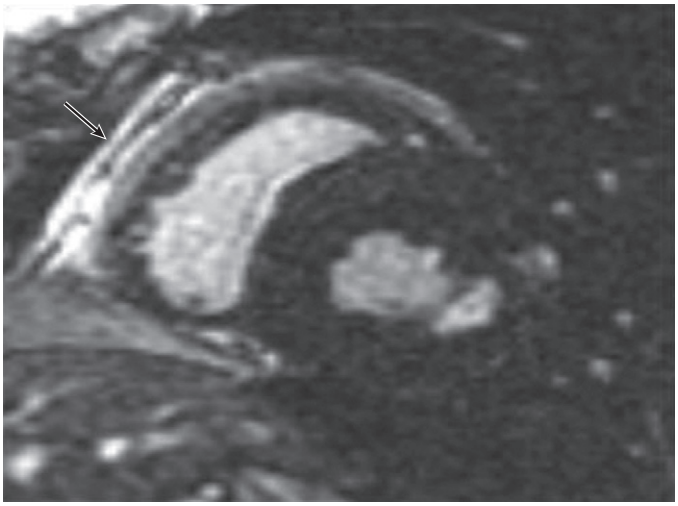

FIGURE 12–8 MRI scan from a patient who presented with MI and normal coronary arteries. Note the area of delayed hyperenhancement (*arrow*), which is indicative of myocardial damage. In this case, there is likely AMI, despite the normal coronary arteries. *(From Tello-Montoliu A, Marin F, Roldan V, et al: A multimarker risk stratification approach to non-ST elevation acute coronary syndrome: Implications of troponin T, CRP, NT pro-BNP and fibrin D-dimer levels. J Intern Med 2007;262:651-658.)*

Recent data, albeit with only one sample per patient, suggests that women are less prone to have elevated cTn levels and more apt to have elevated CRP and/or BNP levels. Of importance is the observation that an elevation of any of these latter biomarkers identifies a group of individuals who might benefit from an invasive therapeutic strategy.[92] More sensitive troponin assays might eliminate this disparity between male and female MI patients[24,99] but, if not, other markers might have an important role.

Biomarkers under development may play a role during follow-up of patients with MI. Inflammatory markers such as CRP and neopterin[108] may have a role here; natriuretic peptides, including BNP and NT–pro-BNP, have also been shown to be of potential help in defining the prognosis of patients with MI, especially those with normal troponin values (see earlier).[109] There is strong evidence documenting the prognostic importance of renal function in patients with MI. The estimated glomerular filtration rate (GFR) is useful but cystatin C appears to provide still better information.[110] This is likely because cystatin C provides a continuous evaluation of renal function, whereas creatinine levels and the calculated GFR do not become abnormal until there are substantial decreases in GFR.[111] How to respond therapeutically to these values is unclear at this time, although it is known that the cystatin C level can be elevated in inflammatory conditions and reduced during anti-inflammatory therapy.

Finally, so-called death markers are being developed. In heart failure patients, natriuretic peptides initially were thought to be the most potent for predicting mortality, but recent data suggest that ST2, a peptide related to interleukin-33, may be still more predictive.[111,112] In addition, a marker known as GDF-15, a member of the transforming growth factor beta superfamily has recently shown robust prognostic significance for predicting mortality in NSTEMI patients. GDF-15 also seems to identify individuals with MI who might benefit from an invasive therapeutic approach. However, how many of these initial reports will actually be translated into clinical reality is unclear at the present time.

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CHAPTER 13

Prognostic Risk Stratification After Acute Coronary Syndromes: The Role of Noninvasive Testing

Bernard R. Chaitman and Jennifer Lash

An acute coronary syndrome (ACS) is comprised of biomarker-positive ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), and biomarker-negative unstable angina (UA; Fig. 13-1).[1] The most common pathology that causes an ACS is disruption of a vulnerable coronary artery plaque and subsequent luminal thrombotic obstruction. Less common causes are coronary vasospasm, spontaneous dissection, and severe demand-induced ischemic processes, such as marked tachycardia or severe hypotension. The treatment strategy for STEMI involves immediate percutaneous coronary intervention (PCI) or fibrinolysis when feasible and appropriate, whereas for NSTEMI-UA (NSTE-ACS) an immediate (early) or selective invasive (conservative) approach is recommended, depending on prognostic indicators during the index event. In this chapter, noninvasive risk stratification for patients who present to the emergency room with chest pain and stabilized ACS patients at or around the time of hospital discharge will be discussed, with emphasis on patients admitted for NSTE-ACS syndromes caused by total or partial thrombotic occlusion on a vulnerable ruptured plaque. It should be noted that risk stratification for ACS patients is an ongoing process that starts when the patient first presents to the health care system and continues for several months after hospital discharge. The reader is referred to other sections in this text for a more detailed description of ACS patient management in the emergency room and the first 24 to 48 hours of hospitalization.

CHEST PAIN EVALUATION IN THE EMERGENCY DEPARTMENT

A major goal in the evaluation of patients with nontraumatic chest pain in the emergency department (ED) is to rule out an acute myocardial ischemic event.[1-3] The initial evaluation requires an assessment of the likelihood that the chest pain or chest pain equivalent (e.g., dyspnea, excessive fatigue) is caused by an ACS and, if so, whether the patient is at low, intermediate, or high risk of an early adverse outcome. Of more than 5,000,000 patients presenting to the ED in the United States annually with chest pain, most (>90% to 95%) do not have electrocardiographic evidence of STEMI, and only a minority (~20%) will rule in for an NSTE-ACS.[2] Among patients discharged with a diagnosis of ACS, the initial ED ECG will show findings suggestive of myocardial ischemia in approximately 40% to 50% of cases. To enhance the sensitivity of the 12-lead electrocardiogram (ECG), serial or continuous electrocardiographic monitoring, and the use of nonstandard lead systems that include posterior and right ventricular leads, can be helpful when the suspicion for ACS is high and the initial ECG is nondiagnostic, with unremarkable cardiac biomarkers.[4] The cost-effectiveness of this strategy for all patients presenting with chest pain to the ED has not been determined, but is not likely to be cost-effective. Clinically low-risk patients with chest pain, who present with stable symptoms and a normal or nondiagnostic ECG, can usually be managed by an accelerated diagnostic protocol that includes 6 to 12 hours of clinical and electrocardiographic monitoring and serial cardiac biomarkers.

Methamphetamine or cocaine-related chest pain is a common problem in the United States, leading to more than 500,000 visits to the emergency department annually; 40% of these patients complain of chest pain. Distinguishing a patient with an ACS who has recently used cocaine can present a diagnostic problem in the ED.[5] Cocaine use causes an acute dose-dependent increase in heart rate, systolic blood pressure, and contractility by blocking catecholamine uptake and constricting coronary arteries, and may be associated with a hypercoagulable state. In one series of 4568 patients evaluated in a chest pain unit in Sacramento, California, the prevalence of coronary disease in patients with a positive drug screen was similar to those with a negative result.[6] Thus, the risk stratification process in a patient with chest pain associated with cocaine abuse should

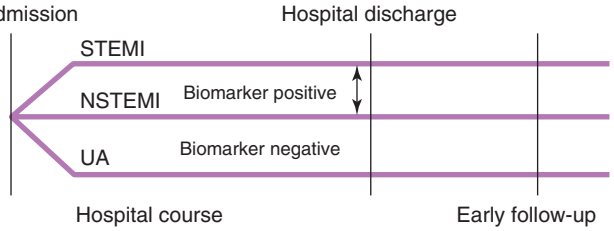

FIGURE 13–1 Risk stratification for the three types of acute coronary syndrome—STEMI, NSTEMI, and UA. This is a continuous process that starts at the time of symptom onset and continues at the time of initial presentation, during the early hospital course, and around the time of hospital discharge. It includes responses to anti-ischemic, antithrombotic, and PCI-CABG therapy.

follow standard established processes for ACS as detailed below.

Rest and Dynamic Electrocardiographic Changes

Baseline demographics and the rest and dynamic ECGs (e.g., Holter, telemetry, monitoring devices) contain important prognostic information that can be used to establish an ACS diagnosis as well as an immediate treatment strategy.[1] Electrocardiographic abnormalities of myocardial ischemia or infarction may be inscribed in the PR segment, QRS complex, and ST segment or T waves. The earliest manifestations of myocardial ischemia are typical T waves and ST-segment changes. Increased hyperacute T-wave amplitude with prominent symmetric T waves in at least two contiguous leads is an early sign that may precede the elevation of the ST segment. Increased R-wave amplitude and width (giant R wave with S-wave diminution) are often seen in leads exhibiting ST elevation and tall T waves, reflecting conduction delay in the ischemic myocardium. Transient Q waves may be observed during an episode of acute ischemia or, rarely, during acute myocardial infarction with successful reperfusion. Q waves indicating prior myocardial infarction almost always confirms the diagnosis of coronary disease and new ST-segment depression ≥0.05 mV in at least two contiguous leads, or T-wave inversion ≥0.01 mV in at least two contiguous leads, with a prominent R wave, is consistent with myocardial ischemia during or after a chest pain episode with ST-segment elevation or depression associated with a worse mortality outcome than T-wave changes (Fig. 13-2).[4] The presence of a new conduction disturbance (e.g., left bundle branch block), or frequent or complex ventricular ectopy, is also associated with an increased likelihood of coronary disease and adverse outcomes. Table 13-1 summarizes studies on the prognostic value of ST-T–wave abnormalities in NSTE-ACS.[7-16] Table 13-2 illustrates that the cardiac event rate increases with increasing magnitude of ST-segment depression; excessive risk is observed with ST-segment depression (STD) ≥0.05 mV.[11] Although more severe STD is a marker of increased short- and long-term mortality, it is also associated with higher risk clinical features and biomarkers. In the GRACE registry, after adjustment for clinically important predictors, the magnitude of STD does not provide incremental prognostic value beyond simple dichotomous evaluation for the presence of STD.[17]

Dynamic electrocardiographic monitoring early in the course of a STEMI is useful to determine the likelihood of reperfusion.[18,19] When ST-segment elevation (STE) recurs after the ST segment has trended toward normal, reocclusion of the infarct-related vessel should be suspected. It is recommended that an ECG be obtained during any chest pain episodes that occur after the index event because symptomatic and silent ECG changes (e.g., STD or STE) are associated

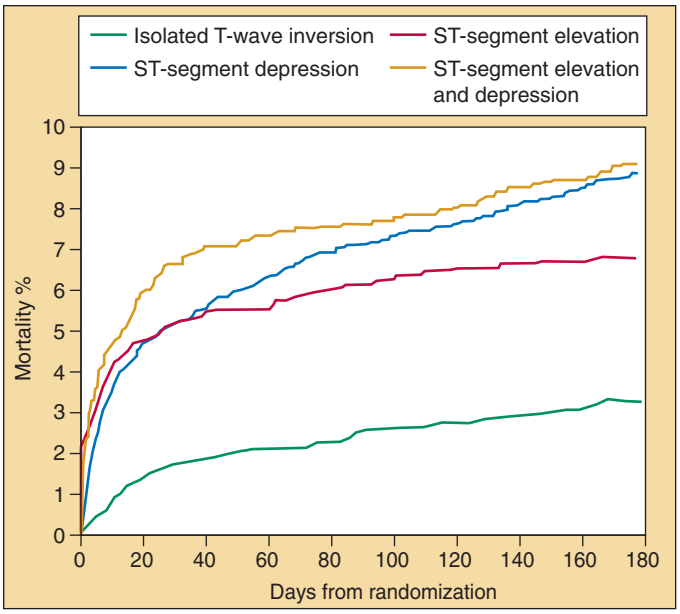

FIGURE 13–2 Kaplan-Meier estimates of probability of death according to ST segment shift or T wave inversion. The mortality risk for T-wave inversion is significantly less than for ST-segment shifts. *(From Savonitto S, Ardissino D, Granger CB, et al: Prognostic significance of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707-713.)*

with a significantly increased risk of reinfarction and death, and is an indication for further investigation and treatment (Fig. 13-3).

Noninvasive Testing in the Emergency Department

An accelerated diagnostic protocol in a patient with suspect ACS stratified to low-intermediate clinical risk may include early exercise testing and/or imaging procedures for risk stratification to determine the need for hospital admission or more intensive monitoring (e.g., cardiac care unit [CCU] admission).[20-28]

Exercise Testing

The use of exercise testing is relatively safe and can identify patients at very low risk for cardiac events.[21-25] Box 13-1 provides indications and contraindications for exercise testing in an ED or chest pain unit. In one series of 1000 clinically low-risk patients presenting to the ED with chest pain between 1993 and 1998, Amsterdam and colleagues[21] performed exercise testing using a modified Bruce protocol and reported that 13%, 64%, and 23% of the exercise tests were normal, abnormal, or nondiagnostic, respectively. There were no deaths in the next 30 days regardless of the exercise test results and those with a normal exercise test were discharged directly from the ED. Of the 640, 125, and 235 patients who had a negative, positive, or nondiagnostic test, a myocardial infarction was diagnosed in 1, 4 and 0 patients, respectively. Similar results have been reported by others and are summarized in an AHA statement on the role of exercise testing for chest pain evaluation in the ED.[25]

Imaging Procedures

Approximately 30% of low-risk patients presenting with chest pain are not candidates for an exercise test. In this setting, stress echocardiography, stress myocardial scintigraphy, or coronary computed tomography (CT) imaging can be used for risk stratification. The addition of left ventricular ejection fraction into risk stratification models improves

TABLE 13–1 Studies on Prognostic Value Of ST-T Abnormalities in NSTE ACS*

Study (Year)	Sample Size	ST-T Criteria on Admission ECG (Prevalence)	Major Findings	Significant Covariate Predictors
ST-T Abnormalities as Univariate Predictor				
Cohen et al (1991)[7]	90†	ST deviation ≥ 1 mm in two or more leads (63%)	Higher 3-mo rates of death, MI, recurrent ischemia, revascularization in the presence of ST changes (77% vs. 36% without ST changes)	N/A
Lee et al (1993)[8]	136‡	ST depression ≥ 1 mm in any lead (100%)	Mortality gradient at 1 yr according to degree of baseline ST depression: 14% (1 mm) vs. 39% (2 mm) vs. 30% (≥3 mm)	N/A
Nyman et al (1993)[9]	911§	ST depression (± T↓) ≥ 1 mm in any lead (24%); isolated T↓ (31%)	Death, MI at 1 yr—7.6% (no ST-T changes) vs. 13.6% (isolated T↓) vs. 18.1% (ST depression)	N/A
ST-T Abnormalities as Multivariate Predictor				
Hyde et al (1999)[10]	367§	ST depression ≥ 0.5 mm in any lead (47%); isolated T↓ ≥ 1 mm in any lead (16%)	ST depression ≥ 0.5 mm but not isolated T↓ significantly predicted lower 4-yr survival	Age, CHF, revascularization
Cannon et al (1997)[11]	1416§	ST deviation ≥ 0.5 mm in any lead (27%); isolated T↓ ≥ 1 mm in any lead (22%)	ST deviation ≥ 0.5 mm but not isolated T↓ significantly predicted death, MI at 1 yr	Age, fibrinolysis within past week, nitrate within past week, LBBB, other major illnesses, poor compliance with follow-up
Kaul et al (2001)[13]	1588‡	ST depression ≥ 1 mm in any lead (43%)	Mortality gradient at 1 yr according to degree of baseline ST depression: 2% (no depression) vs. 7.8% (1 mm) vs. 13.4% (≥2 mm) cerebrovascular disease	Age, COPD, previous MI, CHF, PVD diabetes, previous PTCA, cerebrovascular disease
Antman et al (2000)[12]	1957†	ST deviation ≥ 0.5 mm in any lead (72%)	Risk of death, MI, or urgent revascularization in the presence of ST deviation 1.5 times higher than that without ST deviation	Age, three or more cardiac risk factors, prior CAD, ≥50% stenosis, two or more anginal events in prior 24 hr, use of aspirin in prior week, elevated biomarkers‖
Diderholm et al (2002)[14]	2457†	ST depression ≥ 0.5 mm in any lead (46%); isolated T↓ ≥ 1 mm in any lead (36%)	ST depression ≥ 0.5 mm but not isolated T↓ significantly predicted higher death, MI at 1 yr	Age, diabetes, two or more antianginal medications, TnT ≥ 0.06 mg/L, CHF (or LVEF < 45%), early invasive strategy
Savonitto et al (1999)[15]	6986‡	ST depression ≥ 0.5 mm in any lead (35%); isolated T↓ ≥ 1 mm in any lead (22%)	Death, MI at 6 mo—3.4% (isolated T↓) vs. 8.9% (ST depression), $P < .02$	Age, Killip class, tachycardia, PVD diabetes, previous angina, hypertension, elevated CK on admission
Boersma et al (2000)[16]	9461†	ST depression ≥ 0.5 mm in any lead (50%); isolated T↓ ≥ 1 mm in any lead	ST depression but not T↓ associated with near-doubling of 30-day mortality	Age, heart rate, systolic BP, CHF, elevated CK on admission, prior CABG, diabetes, CCS III/VI angina in past 6 wk, region of enrollment, prior use of beta blocker or CCB

*NSTE ACS encompasses the clinical syndromes of UA and NSTEMI. ST-T changes are described in individual footnotes.
†Part of composite inclusion criteria.
‡Necessary inclusion criteria.
§Not an inclusion criterion.
‖Biomarkers included CK and/or troponin.
CABG, Coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; N/A, not available; PVD, peripheral vascular disease; TnT, troponin T.
From Wong BYL, Fu Y, Armstrong PW: Electrocardiography, ECG monitoring, and provocative stress testing in acute coronary syndromes. In Theroux P (ed): Acute Coronary Syndromes: A Companion to Braunwald's Heart Disease. Philadelphia, WB Saunders, 2003, pp 168-186.

TABLE 13–2 Degree of ST-Segment Depression on Admission Electrocardiogram and Prognosis

Parameter	ST-Segment Depression		
	None	1 mm	≥2 mm
Enrollment MI (%)	28.2	38.8	55.1
Death (%)			
30 days	0.7	2.8	6.3
6 mo	1.1	6.2	12.0
Reinfarction (%)			
30 days	6.8	11.2	14.1
6 mo	8.4	14.1	16.3
Death, re-infarction (%)			
30 days	7.2	12.1	17.1
6 mo	9.2	16.7	23.9

Adapted from Wong BYL, Fu Y, Armstrong PW: Electrocardiography, ECG monitoring, and provocative stress testing in acute coronary syndromes. In Theroux P (ed): Acute Coronary Syndromes: A Companion Textbook to Braunwald's Heart Disease. Philadelphia, WB Saunders, 2003, pp 168-186.

prognostic accuracy in chest pain patients to predict mortality. In the PRISM-PLUS trial, the C statistic was increased from 0.67 to 0.73 by adding ejection fraction to the TIMI risk score in 1104 patients admitted for ACS.[27] The use of a hand-held echocardiographic device to assess left ventricular function was examined by Weston and associates[26] in 150 patients who presented to the ED with suspected ACS. The 30-day incidence of acute myocardial infarction was 2.5% in those with a normal examination and 20% in those with an abnormal test ($P = .002$). Although the hand-held device provides useful information, dobutamine echocardiography is a more robust technique because it is able to induce wall motion abnormalities during stress as well as provide an estimate of resting left ventricular function; it is not as dependent on fortuitously capturing a transient wall motion abnormality if the patient is not ischemic at the time of a rest imaging study. Myocardial perfusion imaging provides similar information as dobutamine echocardiography but is more expensive and results in radiation exposure. Therefore,

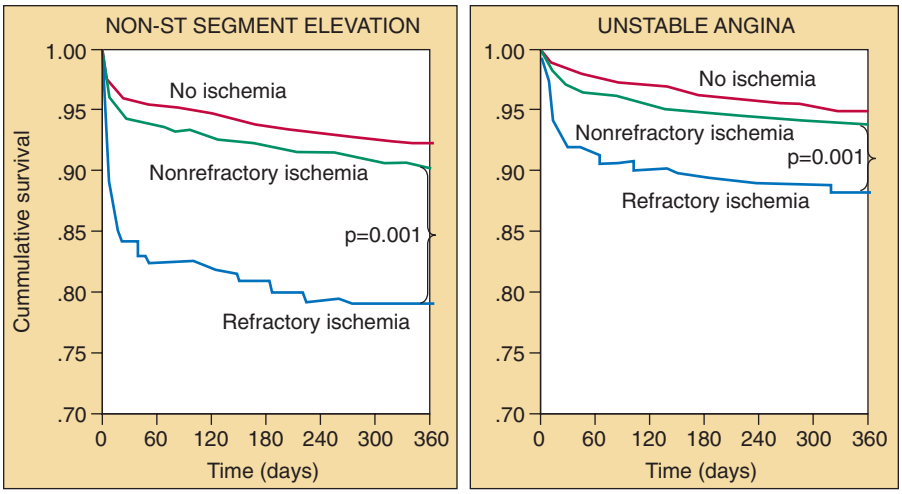

FIGURE 13–3 One-year survival rates among 3513 NSTEMI and 4488 unstable angina patients enrolled in the GUSTO IIb trial by absence and presence of nonrefractory or refractory ischemia. Survival was significantly reduced in both groups ($P < .001$). Nonrefractory ischemia was defined as ischemic symptoms with ST-segment shift or T-wave inversion, and/or new hypotension, pulmonary edema, or ischemic cardiac murmur. Refractory ischemia was defined as symptoms of ischemia with electrocardiographic changes that persisted at least 10 minutes despite anti-ischemic therapy. *(From Armstrong PW, Fu Y, Chang WC, et al; GUSTO-IIb Investigators: Acute coronary syndromes in the GUSTO-IIb trial. Prognostic insights and impact of recurrent ischemia. Circulation 1998;98:1860-1868.)*

BOX 13-1 Indications and Contraindications for Exercise Electrocardiographic Testing in the Emergency Department Setting

Requirements before exercise ECG testing that should be considered in the emergency department setting:

- Two sets of cardiac enzymes at 4-hr intervals—should be normal
- ECG at the time of presentation and pre-exercise 12-lead ECG shows no significant change
- Absence of rest electrocardiographic abnormalities that would preclude accurate assessment of the exercise ECG
- From admission to the time results are available from the second set of cardiac enzymes—patient asymptomatic, lessening chest pain symptoms, or persistent atypical symptoms
- Absence of ischemic chest pain at the time of exercise testing

Contraindications to exercise electrocardiographic testing in the ED setting

- New or evolving electrocardiographic abnormalities on the rest tracing
- Abnormal cardiac enzyme levels
- Worsening or persistent ischemic chest pain symptoms from admission to the time of exercise testing
- Clinical risk profiling indicating imminent coronary angiography is likely

From Stein RA, Chaitman BR, Balady GJ, et al: Safety and utility of exercise testing in emergency room chest pain centers. An advisory from the Committee on Exercise, Rehabilitation and Prevention, Council on Clinical Cardiology, American Heart Association. Circulation 2000;102:1463-1467.

perfusion imaging should be considered when dobutamine echocardiography is not possible because of poor acoustic windows, technically suboptimal images, or a contraindication to dobutamine.

Computed Tomography Coronary Angiography. EBCT (ultrafast CT) is a highly sensitive technique to detect and quantify coronary artery calcification and has been used to triage patients presenting to the ED for chest pain.[20,28-32] Absence of coronary calcification is associated with a low 30-day risk of major cardiac events (<1%). In general, the higher the calcification score, the greater the atherosclerotic burden and likelihood of cardiac events compared with patients without calcification. Limitations of imaging for coronary calcification only are the following: (1) patients with known coronary artery disease usually have coronary calcification and the incremental value of the test in this clinical setting is unlikely to aid in the risk stratification process; (2) EBCT cannot detect vulnerable plaques that do not contain calcium; and (3) approximately 10% of patients with ACS have no calcium detected on imaging. The radiation exposure to patients undergoing EBCT is small.

Contrast-Enhanced Computed Tomography. Contrast-enhanced CT imaging multidetector CT (MDCT) using more than 64-slice scanners have stimulated considerable interest in the ED evaluation of patients presenting with chest pain because the technique provides information on important noncoronary causes of chest pain, such as aortic dissection, pulmonary embolism, and pericardial disease, as well as coronary anatomy and graft patency.[33-38] The images are acquired at a relatively low heart rate (<65 to 70 beats/min). Atrial fibrillation or frequent ectopy diminishes resolution and may result in suboptimal images. The contrast load is at least 60 to 120 mL and may be a relative contraindication in patients with compromised renal function. Radiation exposure can exceed that acquired during coronary angiography. In a relatively small series of clinically low-risk chest pain patients evaluated in the ED or chest pain unit, Goldstein and coworkers have randomized 197 patients to MDCT or a standard diagnostic evaluation. MDCT immediately excluded or identified coronary disease as the source of chest pain in 75% of patients, 67 of whom had normal coronary arteries and 8 of whom had severe disease requiring revascularization.[33] The remaining 25% of the cohort required stress testing for either intermediate lesions or nondiagnostic scans. Diagnostic workup time and cost were significantly decreased using the MDCT approach. In a different series of 92 low-risk chest pain patients, Gallagher and colleagues[28] prospectively studied 30-day event rates using MDCT and myocardial perfusion imaging. Seven (8%) were excluded because of suboptimal MDCT scans. Of the 85 remaining

patients, 7 (8%) had important coronary disease, but none had a major cardiac event. The sensitivity for stress nuclear imaging and MDCT were 71% and 86% of patients, respectively, and specificity was 90% and 92%, respectively, in this small series.

The scientific value of MDCT imaging and its place in the noninvasive evaluation of patients with chest pain in the emergency room is an area of active research. Nevertheless, the number of MDCT procedures performed in the ED to evaluate patients with chest pain has increased rapidly. The MDCT test provides anatomic information but, unlike noninvasive stress test procedures, does not provide a functional assessment of coronary vascular reserve.

ESTABLISHING PRETEST RISK IN ACUTE CORONARY SYNDROME PATIENTS

The pretest risk of a stabilized ACS patient needs to be assessed prior to noninvasive testing to optimize post-test diagnostic and prognostic risk statements. The use of Bayesian principles when applying the results of noninvasive tests to estimate risk is well established.[39] In general, early mortality is greatest in patients who have sustained a STEMI and lowest in those with UA.[1,40] Figure 13-4 illustrates 6-month survival rates for the three different types of ACS in 43,810 patients enrolled in the GRACE registry from 1999 to 2005.[40]

In addition to the type of ACS, numerous demographic characteristics independently predict risk and are incorporated into the different clinical scoring systems used to estimate mortality after an ACS.[41-57] Thus, the 5-year prognostic estimate of mortality for exercise-induced ST-segment depression or an imaging defect at a workload of 5 metabolic equivalent tests (METs) will be different in an older STEMI patient with two prior myocardial infarctions and compensated heart failure (e.g., three-vessel disease and an ejection fraction of 30%) than in a younger patient with no prior cardiac history who presents for the first time with UA (e.g., single-vessel disease and ejection fraction >50%).

The TIMI risk score for STEMI is shown in Figure 13-5 (more information is available at http://www.TIMI.org).[58] Using this risk model, a 65-year-old obese man with anterior ST-segment elevation, a prior history of hypertension and angina but no diabetes, with a normal blood pressure and heart rate and was Killip class lower than 2 at presentation, treated less than 4 hours after symptom onset, would have a risk score of 5 and an estimated 30-day mortality of 12.4%. The pretest risk may be modified lower or higher, depending on the results of noninvasive testing. This concept will be discussed further later in the chapter.

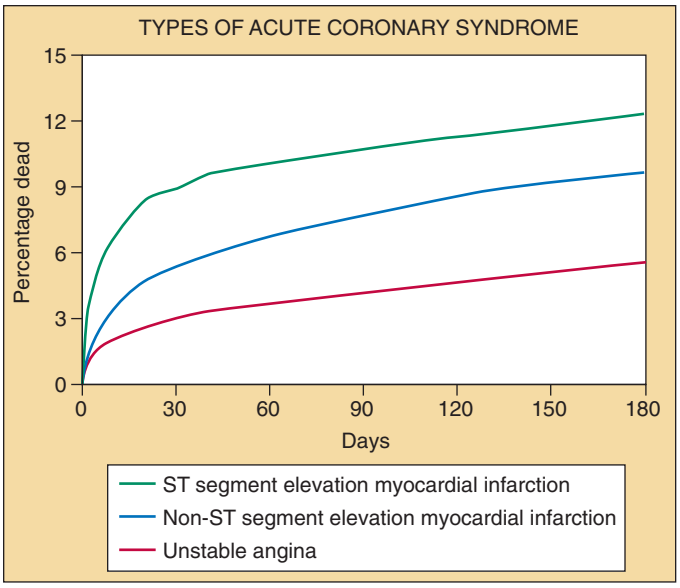

FIGURE 13–4 Risk of death from admission to hospital to 6 months after discharge in the GRACE ACS registry. *(From Fox KAA, Dabbous OH, Goldberg RJ, et al: Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study (GRACE). BMJ 2006;333:1091-1094.)*

Non–ST-Segment Elevation–Acute Coronary Syndrome Risk Scores

Risk scores to stratify NSTE-ACS have been developed by the TIMI, PURSUIT, GRACE, and FRISC groups and by others (Table 13-3).[40,47,49,50,59-65] Goncalves and colleagues[50] studied

HISTORICAL	POINTS MORTALITY	RISK SCORE	*30-DAY*
Age ≥75	3	0	0.8
65-74	2	1	1.6
DM or HTN or angina	1	2	2.2
EXAM		3	4.4
SBP <100 mm Hg	3	4	7.3
HR >100 bpm	2	5	12
Killip II-	2	6	16
Weight <67 kg (150 lb)	1	7	23
PRESENTATION		8	27
Anterior STE or LBBB	1	>8	36
Time to Rx >4 hrs	1		

RISK SCORE = Total points (0-14)

*Entry criteria: CP > 30 min, ST, Sx onset < 6 hr, fibrinolytic-eligible

FIGURE 13–5 TIMI risk score for STEMI. CP, chest pain; DM, diabetes mellitus; HR, heart rate; Rx, treatment; SBP, systolic blood pressure; Sx, symptom. *(From Morrow DA, Antman EM, Charlesworth A, et al: TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation. An intravenous nPA for treatment of infarcting myocardial early II trial substudy. Circulation 2000;102:2031-2037.)*

TABLE 13–3 Risk Scores to Stratify NSTE-ACS

Study	Score (*Separate Points for Enrollment Diagnosis*)
PURSUIT (0-18)	
Age, decade (UA [MI])	
50	8 (11)
60	9 (12)
70	11 (13)
80	12 (14)
Gender	
Male	1
Female	0
Worst CCS class in previous 6 wk	
No angina or CCS class I or II	0
CCS class III or IV	2
Signs of heart failure	2
ST depression on presenting ECG	1
TIMI (0-7)	
Age ≥ 65 yr	1
Three or more risk factors for CAD	1
Use of aspirin (last 7 days)	1
Known CAD (stenosis ≥ 50%)	1
More than one episode rest angina in <24 hr	1
ST-segment deviation	1
Elevated cardiac markers	1
GRACE (0-258)	
Age (yr)	
<40	0
40-49	18
50-59	36
60-69	55
70-79	73
≥80	91
Heart rate (beats/min)	
<70	0
70-89	7
90-109	13
110-149	23
150-199	36
>200	46
Systolic BP (mm Hg)	
<80	63
80-99	58
100-119	47
120-139	37
140-159	26
160-199	11
>200	0
Creatinine (mg/dL)	
0-0.39	2
0.4-0.79	5
0.8-1.19	8
1.2-1.59	11
1.6-1.99	14
2-3.99	23
>4	31
Killip class	
I	0
II	21
III	43
IV	64
Cardiac arrest at admission	43
Elevated cardiac markers	15
ST-segment deviation	30

Adapted from Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R: TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTEACS. Eur Heart J 2005;26:865-872.

460 consecutive Portuguese patients admitted to their CCU for NSTE-ACS from 1999 to 2001 and prospectively tested the predictive accuracy of the TIMI, PURSUIT, and GRACE scores for the composite end point of death or death-MI after 1 year. In their report, each scoring method was effective in identifying low-, intermediate-, and high-risk patients. High-risk patients were classified in 36.7%, 28.7%, and 57.8% of the population using the GRACE, PURSUIT, and TIMI risk scores, respectively. However, receiver operating characteristic (ROC) has analysis determined that the GRACE score has the greatest predictive accuracy in estimating 1-year death-MI. The TIMI and GRACE scores include both the ECG and biomarkers in the model, whereas PURSUIT excludes biomarkers.[61] The FRISC score differs from the other scoring methods by including inflammatory markers in the prediction model (e.g., interleukin-6 or C- reactive protein).[49] An important distinction between the GRACE and other scoring methods is the variable derivation from a registry of consecutive ACS patients rather than a randomized trial that had specific inclusion-exclusion criteria and the inclusion of renal function, a variable known to affect long-term prognosis.[45,47] The validated GRACE prediction model predicts a 6-month mortality risk after hospital discharge in an international registry for all forms of ACS (Fig. 13-6).[47]

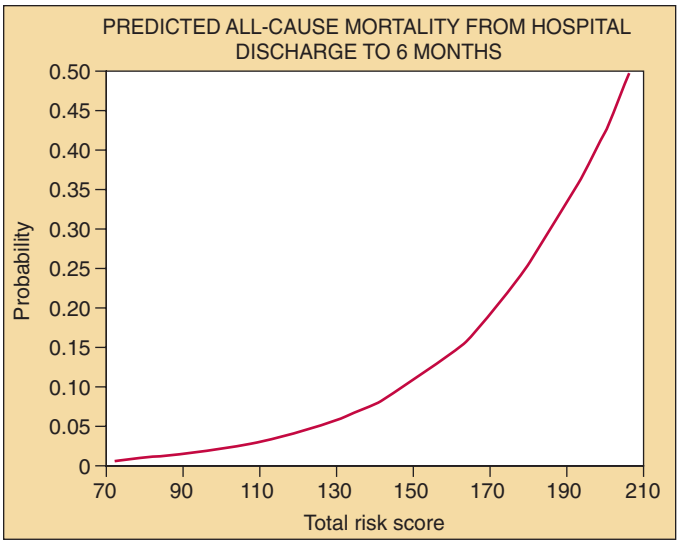

FIGURE 13–6 Predicted all-cause mortality from hospital discharge to 6 months after an ACS in the GRACE registry. *(From Eagle KA, Lim MJ, Dabbous OH, et al; GRACE Investigators: A validated prediction model for all forms of acute coronary syndrome. Estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727-2733.)*

Thus, higher risk patients can be identified early who might benefit from early coronary angiography and revascularization when clinically and technically appropriate or more intensive medical therapy during admission for the index event. For example, patients with important spontaneous silent or symptomatic ischemia after hospital admission, hemodynamic or arrhythmic instability, and severe left ventricular dysfunction (e.g., left ventricular ejection fraction ≤40%) are usually referred for early coronary angiography before noninvasive testing is considered. This means that many patients (but not all) referred for noninvasive testing at or around the time of hospital discharge will be at less than high risk of future cardiac events because higher risk patients are removed early for coronary revascularization. Note that it is the role of the noninvasive test procedures to identify the subset of these patients at lower risk for whom coronary angiography would not be indicated, or the higher risk patients for whom angiography and revascularization or more intensive medical therapy would be indicated to improve life expectancy. Noninvasive testing should not be ordered if the results will not be used to affect subsequent treatment.

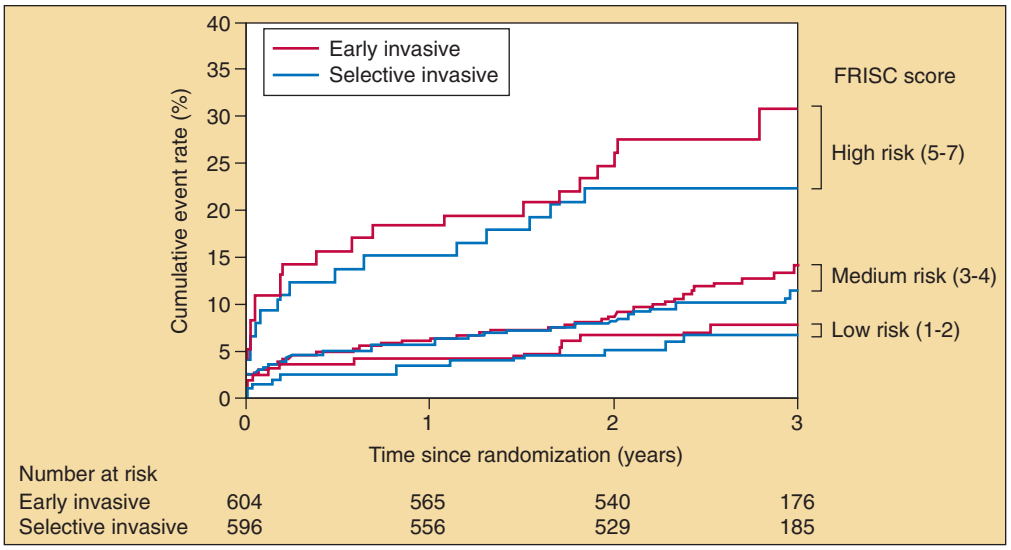

FIGURE 13–7 Cumulative risk of death or spontaneous myocardial infarction by treatment strategy and FRISC score in the ICTUS trial. The FRISC score effectively stratifies NSTE-ACS patients into three risk categories and allows evaluation of treatment strategy according to level of risk. *(From Hirsch A, Windhausen F, Tijssen JG, et al; Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) investigators: Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): A follow-up study. Lancet 2007;369:827-835.)*

The data base for noninvasive testing after MI is robust but the available results and prognostic estimates span several decades in which different treatment regimens and definitions for ACS have been used (Table 13-4).[66-83] This temporal issue affects the ability to extrapolate from earlier studies to contemporary medicine. For example, among the 44,372 patients in the ACS GRACE registry, the 6-month mortality declined from 4.9% in 1999 to 3.3% in 2005 and the recurrent infarction rate from 3% to 1.7%.[84] During this same interval, there was an increased use of aspirin, beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, thienopyridines, and coronary revascularization. This means that post-test estimates of recurrent events will be lower currently than what would have been expected from papers published a decade ago. This is because the highest risk patients have been selected out for procedures that improve life expectancy based on the results of the noninvasive tests (post-test referral bias) and the availability of post-test long-term pharmacologic therapy now reduces cardiac event rates more than at an earlier time (see Table 13-4).

Rationale for Noninvasive Testing Using a Selective Invasive Approach

The rationale for an initially invasive versus a selective invasive (conservative) approach using clinical parameters and noninvasive testing in patients with NSTE-ACS is based on several randomized trials comparing the two treatment strategies. This topic is reviewed in detail elsewhere and in the 2007 American College of Cardiology (ACC)–American Heart Association (AHA) NSTE-ACS guidelines.[1] The RITA-3 trial randomized 1810 British patients with NSTE-ACS to early intervention or a selective invasive strategy within 48 hours of the index episode of cardiac pain, and reported a significant reduction in 5-year cardiac event rates for patients assigned to the invasive strategy.[19] In contrast, the ICTUS trial illustrates why the guidelines state that neither randomized trials nor observational data uniformly support an inherent superiority for the routine initial use of coronary angiography and revascularization in NSTE-ACS patients.[79,80] In the ICTUS trial, 1200 patients with NSTE-ACS, chest pain within the prior 24 hours, an elevated cardiac troponin T level, and either electrocardiographic evidence of ischemia at admission or a documented history of coronary disease were randomized to an early invasive strategy or a selective invasive strategy from 2001 to 2003. Patients with STEMI, age older than 80 years, hemodynamic instability or overt heart failure, oral anticoagulant drugs in the past 7 days, fibrinolytic treatment within the past 96 hours, PCI within the past 14 days or a contraindication to PCI or glycoprotein IIb/IIIa inhibitors, bleeding risk, or uncontrolled hypertension were excluded. Patients assigned to the conservative strategy had revascularization only if they had refractory angina (51% of the group that ultimately received revascularization), hemodynamic or arrhythmic instability (8%), or clinically significant ischemia on the predischarge exercise test (41% of the group that ultimately received a revascularization). Coronary revascularization was performed in 76% and 40% of patients in the early invasive and conservative groups during the initial hospitalization and 79% and 54% after 1 year, with stent usage in 88% of PCI procedures. Early revascularization was performed after a median of 23 hours in the invasive group and after 11.8 days in the 40% of conservative patients who received an early coronary revascularization procedure. The 1-year mortality was 2.5% in both groups. There were no significant differences in the frequency of the primary end point (composite of death, nonfatal MI, or rehospitalization for anginal symptoms) after 3 years in the total population or in subgroups defined according to age, gender, the presence or absence of diabetes mellitus, the presence or absence of ST-segment deviation, or the level of cardiac troponin T.[80] The FRISC prognostic score effectively stratified patients according to risk (Fig. 13-7). There were no significant treatment differences in low, intermediate, or high-risk patients. Thus, at this time, ACC/AHA guidelines recommend that a selective invasive treatment strategy, using noninvasive testing to detect clinically significant ischemia, is a reasonable approach for select patients initially stabilized with NSTE-ACS, particularly those who have lower clinical prognostic risk scores, and for patients or physicians who prefer a selective invasive approach in the absence of high-risk features.

TABLE 13–4 Studies of Noninvasive Tests in Patients with an Acute Coronary Syndrome

Study (Year)	Inclusion Criteria	Exclusion Criteria	Type of Test	Timing After MI	Results of Abnormal Noninvasive Testing	Length of Follow-Up	Outcomes
Theroux et al (1979)[67]	All pts who ruled in based on MI diagnosis criteria	ST elevation on ECG	Treadmill, Naughton protocol	11 days (7-20 days)	Abnormal; angina; horizontal STD ≥ 1 mm; test results did not lead to cath, intervention	1 yr	2.1% mortality with no STD; 27% mortality with STD (*N* = 210)
Wilcox et al (1991)[68]	All pts admitted to CCU with UA; not scheduled for PCI or CABG	≥70 yr of age; history of MI in prior mo; CP in prior 3 days; uninterpretable ECG	Treadmill, modified Naughton	3 days after UA	Abnormal; ≥0.1 mV horizontal or downsloping STD; ≥0.15 mV slow upsloping STD; >0.1 mV additional STD in pts with ≥0.1 mV STD or ≥0.1 mV STE at rest; three pts with positive stress tests went to cath (results unknown)	1 yr	Low-risk ECG associated with lower risk of MACE at 12 mo (*N* = 149)
Nyman et al (1993)[69]	Men <70 yr of age with UA	STE or QS development in two consecutive leads; previous CABG; CK peak >15 ukat/L; uninterpretable ECG; current treatment with aspirin or anticoagulation; persistent CP	Bicycle	3-14 days after admission	Low risk—performed >140 W; 0 leads with ≥0.05 mV STD; high risk—performed <100 W; two or more leads with ≥0.05 mV of STD; no cath for high-risk pts	1 yr	High-risk pts had 1-yr mortality of 3.6% and 1-yr event rate of MI or death of 15.4% compared with low-risk pts with event rate of 0% and 3.9%, respectively (*N* = 855)
Lindahl et al (1997)[70]	Pts > 40 yr of age with chest pain and changes in ECG (STD ≥ 0.1 mV or T-wave inversion)	Premenopausal women; STEMI; LBBB; pacemaker; myocarditis, pericarditis; significant AV disease; cardiomyopathy; severe systemic illness; planned PCI or CABG	Bicycle, symptom-limited	5 days	Low risk—normal maximal workload (>90 W for men and >70 W for women); no STD of ≥0.1 mV in three or more leads; high risk—low maximal workload (<90 W in men and <70 W in women); STD of ≥0.1 mV in three or more leads; no cath in high-risk pts	5 mo	High-risk stress test leads to higher event rates; death or MI occurred in 5% of low-risk stress test pts vs. 29% of high-risk stress test pts (*N* = 766)
Safstrom et al (1998)[71]	Postmenopausal women admitted to CCU with typical CP and changes in ECG (STD ≥ 0.1 mV or TWI)	LBBB; LVH; pacemaker; myocarditis, endocarditis; cardiomypathy; significant AV disease; planned PCI or CABG; severe systemic disease	Bicycle, symptom-limited	5-8 days	≥0.1 mV of downsloping or horizontal STD; cath on all pts within 60 days	3 mo	STD has positive predictive value of 91% for angiographically significant CAD (no prognostic data) (*N* = 176)
TIMI IIIB (1994)[72]	Pts 21-79 yr with ischemic chest pain associated with ≥0.1 mV of ST elevation <30 min; STD ≥ 0.1 mV *or* TWI; documented CAD by cath or positive nuclear test	MI in previous 21 days; angio in previous 30 days; PTCA ≤ 30 days; CABG; pulmonary edema; SBP > 180 or DBP > 100 mm Hg; contraindication to thrombolytics; severe systemic illness; LBBB; oral anticoagulants; women who could be pregnant	Treadmill, modified Bruce protocol	Prior to discharge	Pts went to cath if prior to completing stage II they had ischemic chest pain, ≥0.2 mV of ST deviation, or decrease in SBP > 10 mm Hg; two or more areas of reversible defect on nuclear imaging; increased LHR and one area of reversible defect on nuclear imaging; chest pain ≥ 5 min with ≥0.2 mV of ST deviation in two contiguous leads; >20 min of ≥0.1 mV ST deviation on 24-hr Holter	6 weeks to 1 year	Primary end point death, MI, unsatisfactory ETT at 6 wk; early invasive test met primary end point at 16.2% compared with selectively invasive group at 18.1%; at 1 yr, no difference between death or recurrent MI (*N* = 1473)
Boden et al (1998)[74]	CK-MB > 1.5 × ULN	New Q waves; serious coexisting conditions; ischemic complications mandating cath	Symptom-limited Bruce protocol; treadmill with thallium dipyridamole if METs < 5	Prior to discharge	STD of 2 mm at peak exercise; pts with redistribution defect in one or two vascular territories and increased lung uptake went for cath	23 months	Angio, 30 days, revasc, 30 days, one end point: invasive, 96%, 44%, 30% respectively; noninvasive, 48%, 33%, 27%, respectively; primary end point, death or nonfatal MI at 23 mo (*N* = 920)

FRISC-II (1999)[76]	Pts with symptoms consistent with ischemia, changes in ECG, and positive cardiac enzymes	Increased risk of bleeding, anemia; thrombolytics; PCI within 6 mo; planned PCI or CABG; renal or hepatic insufficiency; severe systemic disease	Bicycle, symptom-limited	Prior to discharge	Pts went to cath if predischarge stress test showed severe ischemia	1 yr	Angio, 7 days; angio, 12 mo; PCI, 12 mo: invasive, 96%, 99%, 44%, respectively; noninvasive, 7%, 52%, 21%, respectively; 1.7% absolute reduction in mortality in invasive group at 12 mo; 5-yr follow-up shows 4.6% absolute risk reduction of primary composite end point of death or MI in invasive group (*N* = 2457)
Cannon et al (2001)[77]	>18 yr of age with anginal chest pain and STD ≥ 0.05 mV, transient STE ≥ 0.1 mV, T-wave inversion = 0.3 mV, increased cardiac enzymes, or history of CAD by cath; history of revascularization or of MI	Persistent STE; PCI or CABG in previous 6 mo; increased risk of bleeding; LBBB; paced rhythm; warfarin; clopidogrel or ticlopidine for more than 3 days prior to enrollment; severe systemic disease	Treadmill, Bruce protocol, (83% with nuclear or echo imaging)	Prior to discharge	Angina and STD ≥ 0.1 mV; STD ≥ 0.2 mV without symptoms; drop in SBP = 10 mm Hg; one large or two small areas of perfusion defect on nuclear imaging; new wall motion abnormality on echo	6 mo	Angio in hospital, angio 6 mo, PCI 6 mo, one end point: invasive, 97%, 98%, 42%, 15.9%, respectively; noninvasive, 51%, 61%, 29%, 19.4%, respectively; primary end point defined as death, nonfatal MI, rehospitalization; decreased risk of primary end point at 6 mo with early invasive strategy (*N* = 2220)
Spacek et al (2002)[78]	Rest ischemic chest pain > 20 min; STD ≥ 0.1 mm or TWI in two contiguous leads; CK-MB > 2× ULN or positive troponin	Unstable chest CP despite medical therapy; cardiogenic shock; acute LBBB, RBBB, or STE; QWMI or thrombolysis in the last month; PCI or CABG < 6 mo; severe systemic disease	Bicycle, symptom-limited	30 days	CP with STD of 2 mm at peak exercise; perfusion defect of at least one vascular territory in pts who could not exercise and had a dipyridamole nuclear stress test	6 mo	Angio, 6 mo, revasc, 6 mo, one end point: invasive, 100%, 73%, 6.3%, respectively; noninvasive, 55%, 39%, 22.4%, respectively; primary end point, death or nonfatal MI (*N* = 131)
Hirsch et al (2007)[80]	Symptoms of ischemia; elevated troponin T ≥ 0.03 μg/L; ischemic changes on ECG or history of CAD	Age < 18 or > 80 yr; STEMI in the last 48 hr; hemodynamic instability; CHF; increased risk of bleeding	Exercise	Prior to discharge	Pts went for angiography if they had refractory angina (51%), hemodynamic or rhythm instability (8%), or ischemia on an exercise stress test prior to discharge (41%)	3 yr	Angio, 3 yr, revasc, 3 yr, one end point: invasive, 99%, 81%, 30%, respectively; noninvasive, 70%, 58%, 26%, respectively; primary end point, death, nonfatal MI, or rehospitalization for angina (*N* = 1200)
Ekstrand et al (1997)[81]	25% NST; 75% STE/Q wave	Decompensated CHF; severe arrhythmia; unable to exercise	Bicycle, submax	11 days	Abnormal exercise ECG with STD ≥ 1 mm	9 yr	Increased risk of mortality with angina and/or STD > 1 mm on submaximal exercise ECG (*N* = 1098)
Madsen et al (1997)[82]	≤69 yr of age with AMI CK-MB 2× ULN, ST deviation or T-wave changes; and/or new Q waves; patients had to be treated with thrombolytics <12 hr after onset of symptoms and angina; or exercise-induced ischemia	Previous MI, PTCA, CABG; received <50% thrombolytic dose; required immediate intervention; drop in SBP with exercise; LBBB or PPM; unable to exercise; systemic illness	Bicycle, symptom-limited	Prior to discharge	Abnormal if STD ≥ 0.1 mV in any lead or STE ≥ 2.0 mV in any lead without Q waves; cath only performed if there was SBP drop; looking at follow-up in those with positive stress and/or angina treated with antianginal agents vs. cath	2.4 yr median	Mortality, reinfarct, UA: invasive, 3.6%, 5.6%, 17.9%, respectively; noninvasive, 4.4%, 10.5%, 29.5%, respectively (*N* = 1008)
Al-Khalili et al (2007)[83]	Women <66 yr of age admitted with MI or UA, 48% Q-wave MI and 52% NQWMI	Unable to exercise; LBBB; ST segment could not be assessed because of RBBB or digitalis effect	Bicycle, symptom-limited	3-6 mo	Abnormal exercise ECG with horizontal STD ≥ 1 mm	9 yr	Decreased exercise tolerance predictor of increased mortality (*N* = 273)

AMI, Acute myocardial infarction; angio, angiography; AV, aortic valve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; cath, catheterization; CHF, congestive heart failure; CK-MB, creatine kinase isoenzyme; CP, chest pain; DBP, diastolic blood pressure; echo, echocardiography; ETT, exercise tolerance test; LBBB, left bundle branch block; LHR, lung heart ratio; LVH, left ventricular hypertrophy; MACE, major adverse cardiac events; MI, myocardial infarction; NST, non-ST (as in NSTEMI); NQWMI, non–Q-wave MI; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; pts, patients; QWMI, Q-wave myocardial infarction; RBBB, right bundle branch block; revasc, revascularization; SBP, systolic blood pressure; STD, ST-segment depression; STE, ST-segment elevation; STEMI, ST-segment elevation myocardial infarction; STE/Q, ST-elevation/Q-wave MI; TWI, T-wave inversion; UA, unstable angina; ULN, upper limits of normal.

Predischarge Noninvasive Test Procedure Considerations

The choice of which noninvasive test procedure to use around the time of hospital discharge is based on the following:

- Patient's ability to exercise
- Whether there are rest electrocardiographic abnormalities such as a paced rhythm, left bundle branch block (LBBB), or other abnormalities that preclude assessment of the exercise ECG
- Whether ventricular function information has not already been obtained
- Whether knowledge of the location of the ischemic territory would be useful (e.g., the patient had an intermediate PCI result for a proximal left anterior descending artery [LAD] lesion and had residual disease in other coronary arteries)
- Local technical expertise
- Availability of the test procedure

The need for noninvasive testing before hospital discharge after PCI for STEMI was examined in the PAMI II trial.[85] In this study, 471 low-risk patients (age <70 years, left ventricular ejection fraction >45%, one- or two-vessel disease, successful percutaneous transluminal coronary angioplasty [PTCA], no persistent arrhythmias) were randomized to receive accelerated care and day 3 hospital discharge without noninvasive testing or traditional care. There were no significant differences in the 6-month mortality (0.8% vs. 0.4%) or reinfarction rates (0.8% vs. 0.4%), or in the incidence of UA or heart failure among treatment strategies. It should be noted however, that there were a relatively small number of deaths and recurrent infarctions and the study may have been underpowered to test treatment differences for these end points. A 6-month follow-up is relatively short to test differences in strategy for ischemic heart disease, and the small benefit observed in the patients who had noninvasive testing compared who those that did not may have been accentuated if follow-up were longer.

In general, patients who cannot perform a predischarge exercise test have a worse prognosis than those than can do the test. For example, in the DANAMI-II STEMI trial, mortality rates after a median of 4.5 years was 48% in the nonexercise group and 9% in the exercise group.[86] Those in the nonexercise group unable to exercise were significantly older, were more frequently women, had a history of heart failure or diabetes and/or worse left ventricular systolic function, and lower body mass index (BMI). Similar findings were reported for NSTE-ACS. In a large German NSTE-ACS registry, 1-year mortality was 13.6% for those unable to perform the exercise test compared with 5.1% in the 1097 patients able to perform the test.[87] Box 13-2, from the ACC/AHA ACS guidelines, provides class I indications for noninvasive testing after an ACS according to pretest clinical risk and type of noninvasive test.[1]

Exercise Testing

Exercise testing after an ACS event is useful for the following: (1) risk stratification and assessment of prognosis; (2) functional capacity for activity prescription after hospital discharge; and (3) assessment of adequacy of medical therapy and the need to use supplemental diagnostic or treatment options.[39] Exercise testing after an MI is relatively safe. The risk is slightly greater when symptom-limited rather than submaximal exercise is performed. A lower level exercise test (achievement of 5 to 6 METs or 70% to 80% of age-predicted maximum) is frequently performed before hospital discharge to establish functional capacity and recommendations for early post-ACS activity prescriptions, assess the hemodynamic response (heart rate, blood pressure) to exercise, and determine the ischemic threshold, if present. Parameters associated with an adverse prognosis include inability to perform or complete the test, poor exercise capacity, inability to increase or decrease in exercise systolic blood pressure, and angina or exercise-induced STD at low workloads. β-Adrenergic blocking drugs may attenuate the ischemic response but do not mask poor functional capacity as a marker of adverse prognosis and should be continued in patients referred for testing.[88] In many medical centers, predischarge exercise testing is performed within 3 to 4 days in uncomplicated patients after acute MI (e.g., absence of recurrent chest pain, heart failure, renal insufficiency, hemodynamic instability, or cardiac arrhythmias). A 3- to 6-week test may be useful in clearing patients to return to work in occupations involving physical labor in which the MET expenditure is likely to be greater than that on a predischarge test. As noted, there are few reports that provide prognostic estimates of long-term morbidity and mortality rates using the exercise ECG from a contemporary data base. This type of data would be confounded by post-test referral bias and would need to

BOX 13-2 ACC/AHA Guidelines for Class I Indications* for Noninvasive Testing After Acute Coronary Syndrome

1. Noninvasive stress testing is recommended for low- or intermediate-risk patients free of ischemia at rest or with low-level activity and of heart failure for a minimum of 12 to 24 hours. *(level of evidence: C)*
2. The choice of stress test is based on the rest ECG, ability to perform exercise, local expertise, and technologies available. Treadmill exercise is useful for patients able to exercise in whom the ECG is free of baseline ST-segment abnormalities, bundle branch block, LV hypertrophy, intraventricular conduction defect, paced rhythm, preexcitation, and digoxin effect. *(level of evidence: C)*
3. An imaging modality should be added for patients with resting ST-segment depression (≥0.10 mV), LV hypertrophy, bundle branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. In patients undergoing a low-level exercise test, an imaging modality can add sensitivity. *(level of evidence: B)*
4. Pharmacologic stress testing with imaging is recommended when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, general debility) preclude adequate exercise stress. *(level of evidence: B)*
5. Prompt angiography without noninvasive risk stratification should be performed for failure of stabilization with intensive medical treatment. *(level of evidence: B)*
6. A noninvasive test (echocardiography or radionuclide angiography) is recommended to evaluate LV function in patients with definite ACS who are not already scheduled for coronary angiography and left ventriculography. *(level of evidence: B)*

Definitions for levels of evidence: A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single randomized trial or nonrandomized studies; C, only consensus opinion of experts, case studies, or standard of care.

*Class I indication: Level of evidence clearly outweighs the risk and the test should be performed.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American college of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, American College of Physicians, Society for Academic Emergency Medicine, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2007;50:e1-157.

be adjusted to measure actual performance for specific noninvasive test variables. Nevertheless, earlier data have revealed that numerous exercise variables are useful to estimate risk (see Table 13-4).

In 1979, Theroux and associates[67] assessed the prognostic value of exercise treadmill electrocardiography limited by severe symptoms, electrocardiographic evidence of ischemia, or achievement of 5 METS or 70% of age-predicted heart rate in 210 stable postinfarct survivors. The 1-year mortality was 2.1% (3/146) in patients without ischemic STD and 27% (17/64) in those with ischemic changes ($P < .001$). After 1 year, 65% of patients who had angina during the test reported angina during follow-up compared with 36% who denied angina during the test ($P < .001$). Although this study was performed more than 30 years ago, it illustrates how exercise testing can be used to predict outcomes in an era before the widespread use of test result findings to determine therapy (i.e., before post-test referral bias is established). The use of symptom limited exercise testing after NSTE-ACS was tested in eight Swedish hospitals from 1985 to 1989 in 740 men with an interpretable rest ECG and absence of major left ventricular dysfunction in the RISC trial.[89] Predischarge symptom-limited bicycle ergometry testing was done 5 to 14 days after the index event, starting at 10 W/min and increasing by 10 W/min. Beta blockers (used in 80% of patients) were not stopped prior to testing. The 1-year cardiac mortality was 0.9% in 221 patients with no STD or chest pain (29.9%), 1.4% in 145 patients with chest pain but no STD (19.5%), 4.2% in 144 patients with STD and no chest pain (19.5%), and 3.5% in 230 patients with both STD and chest pain (31%).

The DANAMI-II STEMI trial that compared PCI with thrombolysis reported a four-variable clinical and exercise score that stratified 8% of their population into a high-risk group with a 46% 6-year mortality, 13% into an intermediate risk category with a 16% 6-year mortality, and 79% into a low-risk category with a 4% 6-year mortality.[90] The DANAMI score assigns 1 point for age older than 65 years for men or older than 70 years for women, 1 point for history of new signs or symptoms of heart failure, 1 point for ejection fraction less than 40%, and 1 point for exercise capacity less than 5 METS in men or less than 4 METS in women using bicycle ergometry starting at 25 W and increasing by 25 W every 2 minutes. An ischemic electrocardiographic response was not predictive of death or reinfarction in DANAMI-II.

Imaging Procedures

Imaging procedures are recommended for patients with baseline electrocardiographic abnormalities such as LBBB, paced rhythm, left ventricular hypertrophy, digitalis therapy, or marked repolarization changes (e.g., STD > 1 mm) that compromise interpretation of the exercise electrocardiographic tracing (Box 13-3; see Box 13-2).[91,92] When exercise stress is not possible or compromised (e.g., deconditioning, orthopedic or neurologic impairment), then pharmacologic imaging with dobutamine can be performed with supplemental atropine if necessary to achieve an adequate heart rate response, or coronary vasodilators such as adenosine or dipyridamole can be used when myocardial perfusion imaging is performed.

In patients with a good acoustic window and images, stress echocardiography is preferable to myocardial perfusion imaging because it is less expensive and does not expose the patient to radiation. Exercise stress to a level that adequately tests cardiac reserve is generally preferable to pharmacologic imaging because exercise provides information about the hemodynamic response to work and reproduces physical activities of daily life in a supervised environment, which can be useful in exercise prescriptions after hospital discharge.

BOX 13-3 Risk Stratification Using Noninvasive Testing

High-Risk Findings
- Severe resting LV dysfunction (LVEF < 0.35)
- Exercise-induced ischemia (chest pain or abnormal ECG) at low workloads (<4 METs)
- Severe exercise LV dysfunction (exercise LVEF < 0.35)
- Stress-induced large perfusion defect (particularly if anterior)
- Stress-induced multiple perfusion defects of moderate size
- Large, fixed perfusion defect with LV dilation or increased lung uptake (^{201}Tl)
- Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (^{201}Tl)
- Echocardiographic wall motion abnormality (involving more than two segments) developing at low dose of dobutamine (≤10 μg/kg/min) or at a low heart rate (<120 beats/min)
- Stress echocardiographic evidence of extensive ischemia

Intermediate-Risk Findings
- Mild to moderate resting LV dysfunction (LVEF = 0.35 to 0.49)
- Exercise-induced ischemia (chest pain or abnormal ECG) at intermediate workloads (>4 and < 7METs)
- Stress-induced moderate perfusion defect without LV dilation or increased lung intake (^{201}Tl)
- Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤two segments

Low-Risk Findings
- Good exercise capacity (>7 METs) without evidence or with minor evidence of ischemia
- Normal or small myocardial perfusion defect at rest or with stress*
- Normal stress echocardiographic wall motion or no change of limited resting wall-motion abnormalities during stress*

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting left ventricular dysfunction (LVEF < 35%).

Adapted from Gibbons RJ, Abrams J, Chatterjee K, et al; ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina). Available at: http://www.acc.org/qualityandscience/clinical/guidelines/stable/stable_clean.pdf.

Exercise Echocardiography. Echocardiography can be used to assess right and left ventricular function and myocardial viability.[92-95] This topic is reviewed in depth elsewhere (see Chapter 14). After an MI, many patients will have a resting wall motion abnormality. Hypokinetic, akinetic, or dyskinetic wall motion at rest may indicate necrosis or a stunned or hibernating myocardium. Hyperdynamic wall motion after exercise or dobutamine in noninfarct zones provides indirect evidence of adequate coronary vascular reserve. Detection of a new wall motion abnormality at a site distant from the site of prior infarction suggests multivessel disease. The larger the wall motion abnormality, the greater is the amount of myocardium in jeopardy. More severe stress-induced wall motion abnormalities (e.g., dyskinesis vs. moderate hypokinesis), are associated with a more severe myocardial ischemic response.

The ability to risk-stratify low-risk patients with suspected NSTE-ACS (diagnosis not confirmed by coronary angiography) with echocardiography has been tested in a study of 433 British patients with a nondiagnostic ECG, negative troponin, and more than two risk factors.[93] In this study, from 2003 to 2004, the patients were randomized to a Bruce treadmill protocol ECG or stress echocardiography, using treadmill or dobutamine as the stressor. The stress echocardiogram as

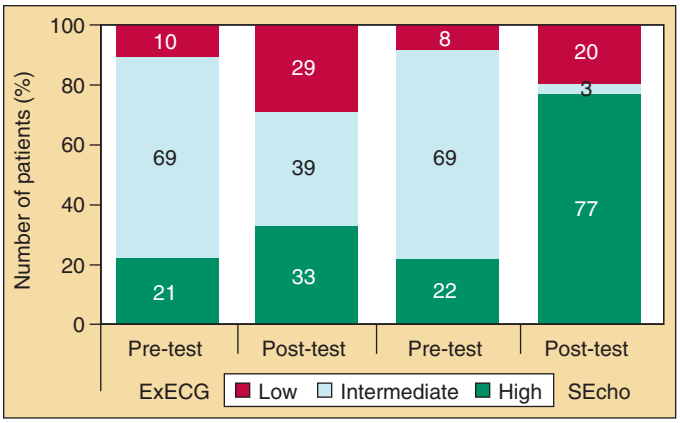

FIGURE 13–8 Patients (%) with a nondiagnostic ECG, negative troponin, and more than two risk factors evaluated for ACS stratified into low-, intermediate-, and high-risk prognostic categories according to the exercise ECG alone or with exercise imaging using echocardiography. The addition of echocardiographic imaging allocates patients into lower and higher risk categories more effectively and reduces the number of intermediate-risk patients. *(From Jeetley P, Burden L, Stoykova B, Senior R: Clinical and economic impact of stress echocardiography compared with exercise electrocardiography in patients with suspected acute coronary syndrome but negative troponin: A prospective randomized controlled study. Eur Heart J 2007;28:204-211.)*

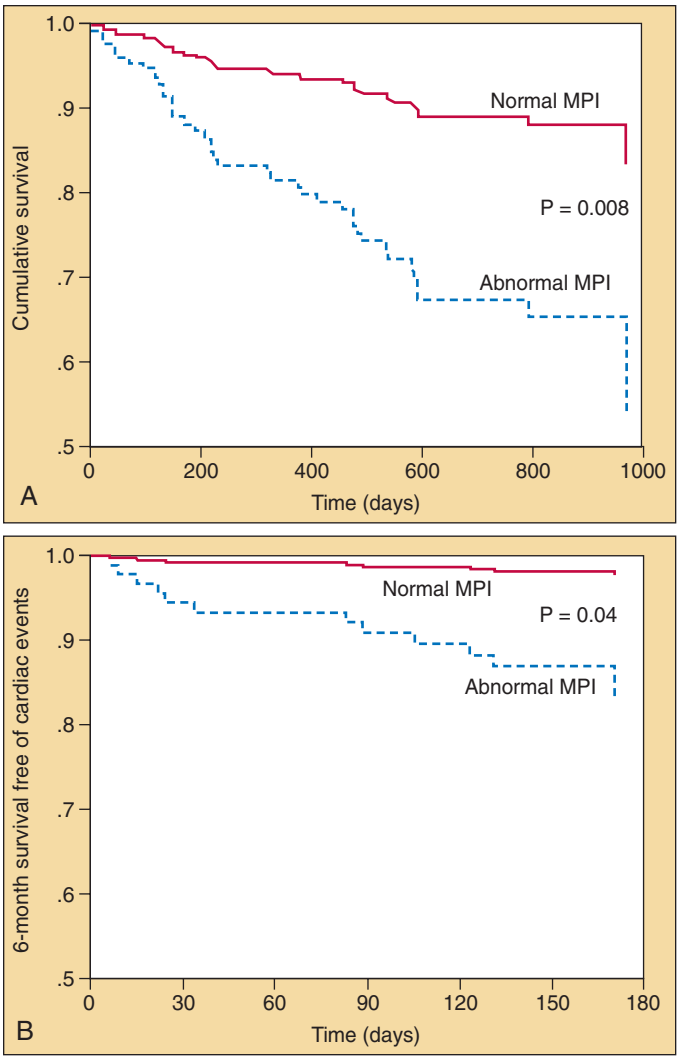

FIGURE 13–9 Risk-adjusted survival curves for overall survival **(A)** and 6-month survival free of cardiac events **(B)** in patients with normal compared with those with abnormal stress MPI results in low-intermediate–risk NSTE-ACS patients (TIMI risk score < 5) with elevated cardiac TnI levels. *(From Dorbala S, Giugliano RP, Logsetty G, et al: Prognostic value of SPECT myocardial perfusion imaging in patients with elevated cardiac troponin I levels and atypical clinical presentation. J Nucl Cardiol 2007;14:53-58.)*

compared with the exercise electrocardiographic protocol classified significantly more patients to the low-risk (77% vs. 33%) and high-risk (29% vs. 20%) categories and reduced the number of patients in the intermediate-risk category (3% vs. 39%; Fig. 13-8).

The number of end points in this study was too small to test prognosis with only 2 non-cardiac deaths and 8 infarcts but illustrates the point that noninvasive testing using stress echocardiography can clearly move clinically lower risk patients to even lower or higher clinical risk patient subsets that would not or would potentially benefit from coronary revascularization or more intense medical management.

Myocardial Perfusion Imaging. Stress myocardial perfusion imaging (MPI) with thallium-201 (^{201}Tl) or technetium-99m (^{99m}Tc) sestamibi provides similar information as echocardiography in terms of risk stratification after an ACS.[91] Therefore, the choice of imaging modality will depend in part on patient characteristics, cost, availability, and local expertise. In patients with a poor acoustic window or, in some cases, when the distribution of the ischemic territory cannot be adequately assessed with echocardiography, stress MPI is preferred. Whereas stress echocardiography provides indirect evidence of coronary vascular reserve, MPI provides a more direct approach to assess coronary perfusion. Like echocardiography, MPI can be used to assess myocardial viability, ventricular function, and myocardial perfusion.[96-100] The prognostic value of MPI after an NSTE-ACS was tested by Dorbala and coworkers[96] in 156 patients with low-intermediate risk NSTE-ACS (TIMI risk score <5), and elevated cardiac troponin I (cTnI) levels who underwent rest-stress ^{99m}Tc-sestamibi MPI. Of the 156 patients, 61% had an abnormal test result. Survival curves adjusted for dyslipidemia, cTnI level, and coronary revascularization performed within 6 months revealed that an abnormal MPI and renal insufficiency were significant predictors of cardiac death or recurrent myocardial infarction. In contrast, a normal MPI, observed in 39% of patients with elevated cTnI, was associated with a more favorable event-free survival (Fig. 13-9).

Erne and colleagues[101] studied 201 asymptomatic Swiss patients with exercise-induced silent myocardial ischemia on a bicycle ergometry study within 3 months of a first ACS admission between 1991 and 1997 in the SWISS II trial to determine the role for PCI in this setting. All subjects had silent exercise-induced ischemic ST-segment depression confirmed by stress imaging. Eligible patients with one- or two-vessel disease were then randomized to PCI or intensive anti-ischemic drug therapy. After a 10.2-year follow-up, cardiac death occurred in 3 and 22 patients in the PCI and drug therapy groups (P = .01) and nonfatal recurrent MI in 11 and 40 patients, respectively (P = .002). The benefit only became apparent after 2 years of observation, reinforcing the importance of longer term follow-up when testing treatment strategies in a chronic disease process such as atherosclerosis. This trial illustrates how noninvasive testing may select higher risk patients who may benefit from a revascularization procedure.

Advanced Imaging Techniques. In addition to older, more established techniques of myocardial imaging, cardiac positron emission tomography (PET), cardiac computed tomography angiography (CTA), and cardiac magnetic resonance imaging (MRI) have been applied to evaluate patients after an ACS.[102-114]

Positron Emission Tomography. PET can be used to measure coronary blood flow, assess myocardial viability, and estimate prognosis.[113,114] There are no long-term follow-up studies that used PET to risk-stratify large numbers of patients after an ACS. Fluorodeoxyglucose (FDG)-PET is a more robust technique than ^{99m}Tc-sestamibi or ^{201}Tl–single-photon emission computed tomography (SPECT) to determine myocardial viability.

Multislice Computed Tomography. MSCT has a high correlation to invasive coronary angiography in detecting coronary disease and extent.[102-107] Meijboom and associates[105] performed MSCT using a 64-slice multidetector scanner in 104 patients with NSTE-ACS and compared the results with invasive coronary angiography. MSCT had a sensitivity of 100% and specificity of 75% in predicting luminal narrowing of 50% or more. No long-term follow-up studies have used MSCT to risk-stratify large numbers of patients after an ACS.

Magnetic Resonance Imaging. There are few studies that have assessed MRI in the setting of ACS.[107-112] The technology allows assessment of wall motion abnormalities and global ventricular function at rest and during stress with exercise or pharmacologic agents, such as dobutamine or adenosine. Viable myocardium can be differentiated from dead myocardium by late hyperenhancement after gadolinium. For exercise imaging, an MRI-compatible reclining bicycle is used. Perfusion is assessed by first-pass enhancement by gadolinium into myocardial tissue at rest and during stress. Segmental myocardial assessment can be determined using cine imaging at rest, low-dose dobutamine, or exercise, and at peak heart rate or exercise workload. Hundley and coworkers[115] studied 279 stable outpatients with poor acoustic windows using dobutamine cardiac MRI. After 20 months, in multivariate analyses, patients with inducible ischemia or an ejection fraction (EF) lower than 40% had a significantly increased risk of MI, cardiac death, coronary artery revascularization, UA, or congestive heart failure requiring hospitalization. In another series of 44 ACS patients, cardiac MRI was compared with troponin T (TnT) 96 hours after acute infarction (STEMI = 23 patients, NSTEMI = 21 patients).[111] The extent of infarcted myocardium correlated with peak TnT measurements. Similar data exist for cardiac MRI comparisons to ^{99m}Tc-sestamibi SPECT early after acute MI (7 ± 2 days). In a small series that evaluated prognosis, 144 patients with prior MI (25% acute) were followed for 29 months after a cardiac MRI with gadolinium.[112] Infarct size and peri-infarct ischemia were associated with increased mortality after adjustment for age and left ventricular EF.

Noninvasive Testing for Potentially Lethal Cardiac Arrhythmias

Sudden cardiac death after acute MI continues to be a significant clinical problem, more frequent in survivors with an EF lower than 40%, who should be evaluated for an intracardiac defibrillator (ICD) when indicated.[116] However, sudden cardiac death episodes occur in postinfarct survivors with more preserved left ventricular function and screening electrocardiographic techniques such as heart rate variability studies to detect abnormal autonomic nervous system dysfunction, heart rate turbulence studies to assess baroreflex sensitivity, and microvolt T-wave alternans (TWA) to determine if higher risk patients can be identified who would be candidates for an ICD.[117-119] Ikeda and colleagues[118] enrolled 1,041 Japanese postinfarct survivors with an EF ≥ 40% between 1999 and 2004 to assess the predictive value of ventricular late potentials, ambulatory electrocardiography, and exercise TWA, performed an average of 48 days postinfarction. After 32-month follow-up, an abnormal TWA study, ventricular late potentials, and nonsustained ventricular tachycardia were independent predictors of sudden cardiac death or life-threatening cardiac arrhythmias. The hazard ratio for the end point was 19.7 for TWA, which had the greatest prognostic accuracy compared with the other tests used to determine arrythymogenic potential.

Exner and associates[119] studied 322 patients within 1 week of ACS with an EF lower than 50% to examine heart rate turbulence (HRT) and microvolt TWA in the REFINE trial. After 8 weeks, the median EF significantly increased, from 40% to 47%. Serial testing revealed that cardiac death or resuscitated cardiac arrest could be predicted after the 10- to 14-week test, whereas the tests were unreliable earlier 2 to 4 weeks after the myocardial infarct. The relative risk of cardiac death or resuscitated cardiac arrest was 5.2-fold higher in the group that had impaired HRT and abnormal exercise TWA after a median 47-month follow-up. Currently, although microvolt TWA tests are reimbursable in the United States, the test is not widely applied for the evaluation of postinfarct survivors. This could change if additional research demonstrates that the use of this risk stratification technology identifies higher risk patients who would benefit from ICD or pharmacologic therapy to reduce arrhythmic deaths.

SUMMARY

Noninvasive testing around the time of hospital discharge can clearly move clinically lower risk patients to even lower or higher clinical risk patient subsets that might benefit from coronary revascularization. There are very few studies that directly compare stress echocardiography with stress MPI in a sizeable cohort of stabilized ACS patients, and even fewer using advanced cardiac imaging modalities. There are no major randomized trials that test the hypothesis that routine noninvasive testing at or around the time of hospital discharge results in improved long-term event-free survival in cohorts of patients with different types of ACS that have received early invasive versus selective invasive revascularization. Clinical recommendations from currently available data bases and guidelines indicate that all less than high-risk ACS patients managed with a selective invasive (conservative) approach should have routine noninvasive testing done to identify those who might benefit from coronary angiography and revascularization when clinically appropriate (Fig. 13-10). The clinically high-risk patients have stratified themselves into a higher risk group for whom early coronary angiography would be indicated. In patients who have undergone a revascularization procedure during the index procedure, noninvasive testing should be considered when the patient is not at low clinical risk of cardiac events. The noninvasive test data obtained around the time of hospital discharge can be correlated with the recently acquired coronary angiographic and ventriculographic data and serve as a baseline for future noninvasive tests to determine whether important serial changes have occurred over time. Furthermore, noninvasive testing provides incremental functional data that adds to the anatomic data provided by a two-dimensional coronary angiogram because functional testing measures induced stress-induced global ischemic burden. Luminal narrowing in a two-dimensional angiogram is only a rough estimate of the coronary atherosclerosis extent and marked abnormal noninvasive test results in an otherwise unremarkable angiogram may lead to changes in therapy that could affect longer term prognosis. Sudden cardiac death from nonischemic cardiac arrhythmias is an important contributor to total mortality after an ACS in patients with infarcted myocardium and relatively preserved left ventricular function. Screening techniques such as microvolt TWA require additional research before being recommended as a routine postinfarct screening procedure.

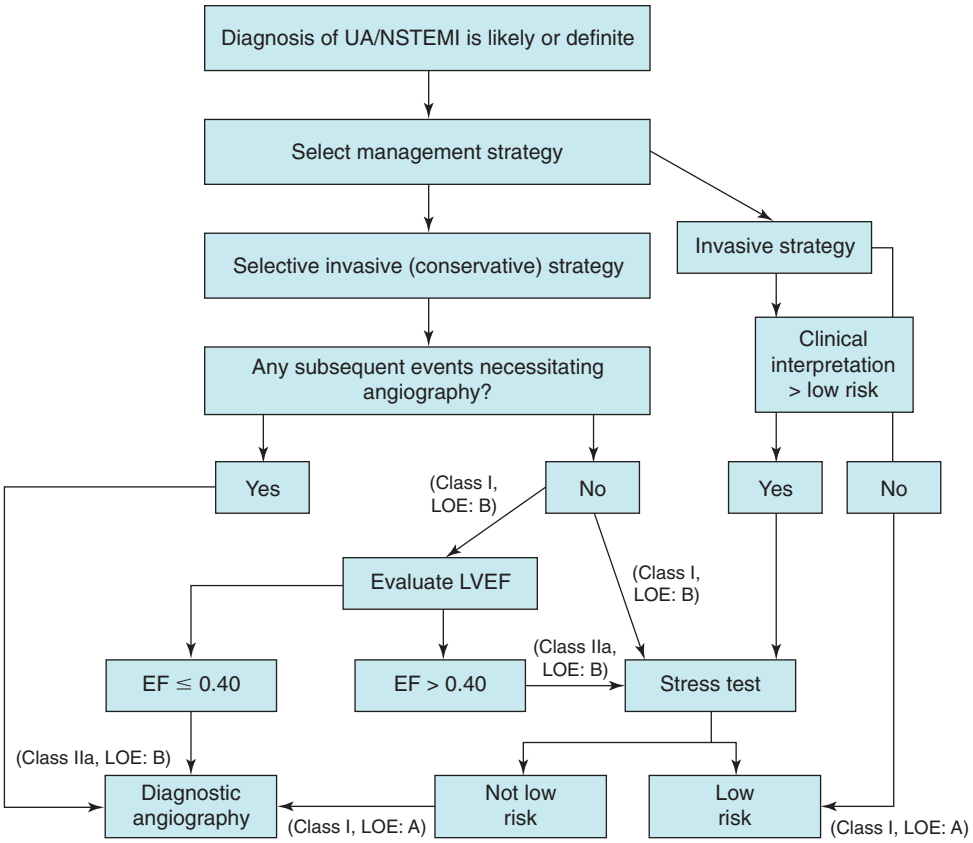

FIGURE 13–10 ACC/AHA 2007 algorithm for patients with UA-NSTEMI managed by an initial selective invasive (conservative) strategy. Patient selection should be based on clinical characteristics such as severity of spontaneous or induced myocardial ischemia, ventricular function, and suitability for a myocardial revascularization procedure. LOE, level of evidence. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 2002 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society of Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:e1-e157.)*

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CHAPTER 14

Echocardiography in Acute Coronary Syndromes

Ariel Diaz, Anique Ducharme, and Jean-Claude Tardif

Given the high prevalence of coronary artery disease (CAD), the evaluation of patients with suspected or documented ischemic heart disease is one of the most common indications for echocardiography. History taking and physical examination in a patient suspected of having CAD remain central to the diagnostic process. Echocardiography, as a rapid, noninvasive, ambulatory, and inexpensive modality, has a unique role, however, in diagnosing CAD, assessing the extent and severity of the disease, and providing important prognostic information that can decisively affect the therapeutic approach. The echocardiographic evaluation focuses on the functional outcome of CAD, global and segmental wall function, and complications of myocardial infarction (MI). This chapter focuses on the use of echocardiography for the diagnosis and management of suspected or proven acute coronary syndrome (ACS).

SEQUENCE OF EVENTS IN MYOCARDIAL ISCHEMIA

Ischemia results from an abnormal myocardial oxygen supply-to-demand ratio. Blood flow is usually adequate for myocardial oxygen demands at rest, unless there is critical (>90% diameter stenosis) coronary artery narrowing. Imbalance occurs in the presence of a physiologically significant stenosis when oxygen demand is increased, as with exercise, mental stress, or pharmacologic interventions, or when myocardial perfusion is reduced by subtotal or total coronary occlusion secondary to atherothrombosis.[1] The first abnormalities to take place (Fig. 14-1) when coronary blood flow is insufficient to meet myocardial demand are cellular biochemical changes, followed by a perfusion defect, diastolic dysfunction (characterized by abnormalities of ventricular relaxation or compliance) and, shortly afterward, impairment of regional systolic wall thickening and motion. The ischemic electrocardiogram (ECG) changes and clinical symptoms of angina (if they appear) are late manifestations of ischemia.[2] Given this sequence of events, echocardiography represents a unique and sensitive tool for early detection of myocardial ischemia, particularly by its ability to identify regional wall motion abnormalities.

EVALUATION OF SYSTOLIC FUNCTION IN ACUTE CORONARY SYNDROMES

Qualitative and Semiquantitative Evaluation of Regional and Global Systolic Function

Global and regional ventricular function can be evaluated with echocardiography. Global systolic function can be qualitatively classified as normal or mildly, moderately, or severely reduced, but this information is considered incomplete by most clinicians. With ventricular contraction, a target point chosen along the endocardial surface moves inward, toward the center of the ventricle (endocardial excursion); the cavity area decreases (area shrinkage), and the distance between the endocardial and epicardial interfaces increases (wall thickening). A few seconds after coronary occlusion, a decrease in the amplitude of endocardial excursion and wall thickening becomes apparent in the area supplied by the obstructed artery.[3] The abnormality is defined as hypokinesis when contraction is normally directed but reduced in magnitude, akinesis when it is absent, or dyskinesis when there is systolic bulging.

Semiquantitative assessment of regional left ventricular contraction is provided by the wall motion score index (WMSI). The left ventricle is divided into 16 or 17 (for perfusion studies) segments (Fig. 14-2), as suggested by the American Society of Echocardiography.[4] A score is assigned to each segment according to its contractility, as follows: normal or hyperkinesis = 1, hypokinesis = 2, akinesis (negligible thickening) = 3, dyskinesis (paradoxic systolic motion) = 4, and aneurysmal (diastolic deformation) = 5. There is no specific score for compensatory hyperkinesis. The WMSI is equal to the sum of the regional scores divided by the number of evaluable segments and can vary

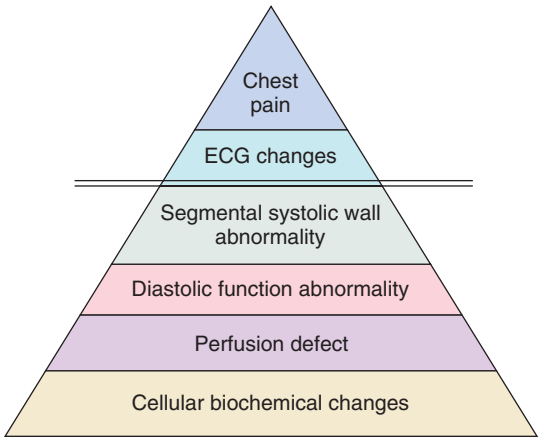

FIGURE 14–1 The sequence of events during myocardial ischemia. ECG, electrocardiogram.

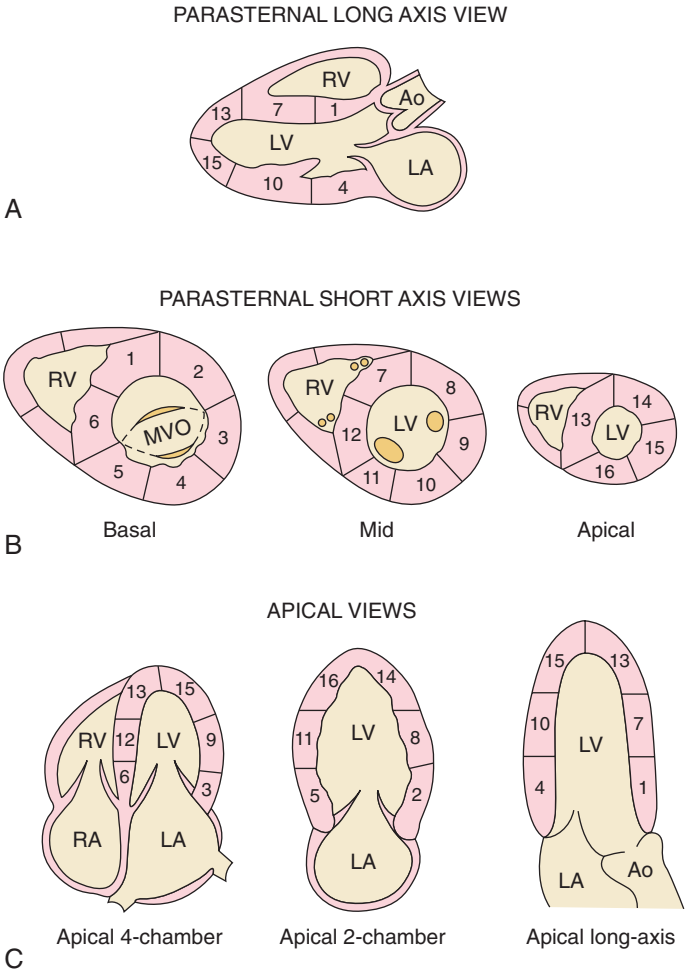

FIGURE 14–2 Schematic of the 16 segments of the left ventricle, as described by the American Society of Echocardiography. **A**, Parasternal long-axis view. **B,** Parasternal short-axis views. **C,** Apical views. The numbers in the diagram correspond to the following segments: 1, basal anteroseptum; 2, basal anterior wall; 3, basal anterolateral wall; 4, basal inferolateral wall; 5, basal inferior wall; 6, basal inferior septum; 7, midanterior septum; 8, midanterior wall; 9, midanterolateral wall; 10, midinferolateral wall; 11, midinferior wall; 12, midinferior septum; 13, septal apex; 14, anterior apex; 15, lateral apex; 16, inferior apex. Ao, aorta; LA, left atrium; LV, left ventricle; MVO, mitral valve orifice; RA, right atrium; RV, right ventricle.

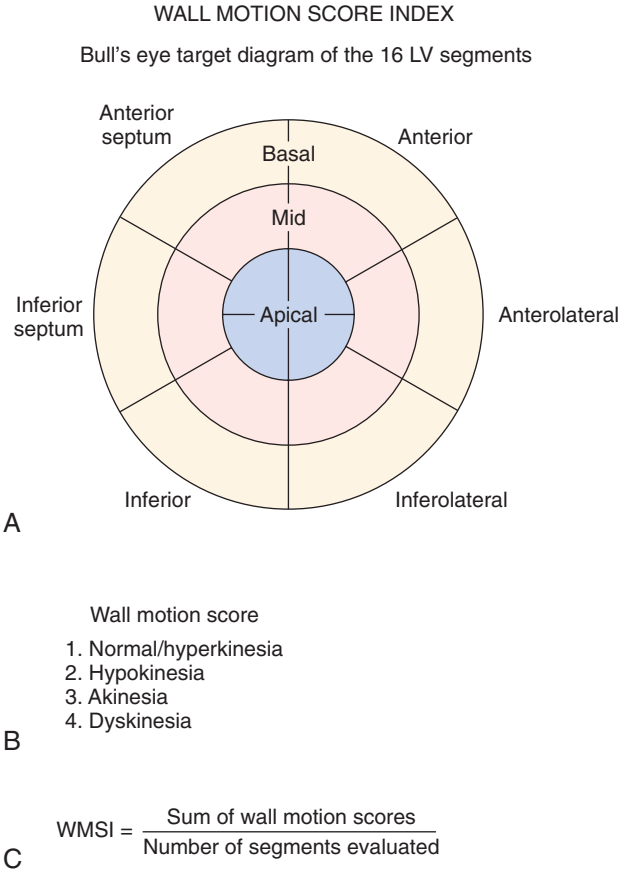

FIGURE 14–3 **A,** The 16 segments of the left ventricle displayed as a bull's eye. **B,** The wall motion score, which assigns a number according to the contractile function of each segment. **C,** The wall motion score index (WMSI) is obtained by dividing the sum of the scores of evaluable segments by the number of segments evaluated.

between 1 (for normal ventricular contraction) and 3.9 (for severe systolic dysfunction; Fig. 14-3). A WMSI of 1.7 usually suggests dysfunction involving more than 20% of the left ventricle after acute myocardial infarction (AMI).[5] The prognostic value of the left ventricular (LV) WMSI has been shown in clinical studies. Among a group of patients admitted with AMI, patients with favorable indices (best quintile) had an incidence of cardiovascular death of 8% at 1 year, whereas patients with the worst quintile had 51% mortality at 1 year.[6] The increase in the odds ratio for in-hospital complications (e.g., death, arrhythmias, heart failure) was 1.20 for each 0.2-unit increase in the WMSI (95% confidence interval [CI], 1.10 to 1.27; $P < .001$).[6] Similar results have been published by Kan and colleagues with a significantly higher mortality rate in the group with the most abnormal score compared with patients with favorable ones (61% versus 3%).[7] In addition, another study in post-MI patients has shown a good correlation between the echocardiographic WMSI and the left ventricular ejection fraction measured by radionuclide ventriculography.[8]

Because CAD causes segmental dysfunction, which can be accompanied by compensatory hyperkinesis of nonischemic segments, regional assessment of systolic function is more sensitive for the detection of ischemia than global approaches. Nevertheless, determination of the left ventricular ejection fraction (LVEF) is part of a standard examination. The correlation between the visual echocardiographic estimation and radionuclide determination is good, especially in patients with an impaired ejection fraction.[9] The eyeball method requires experience, however, and clinicians should validate

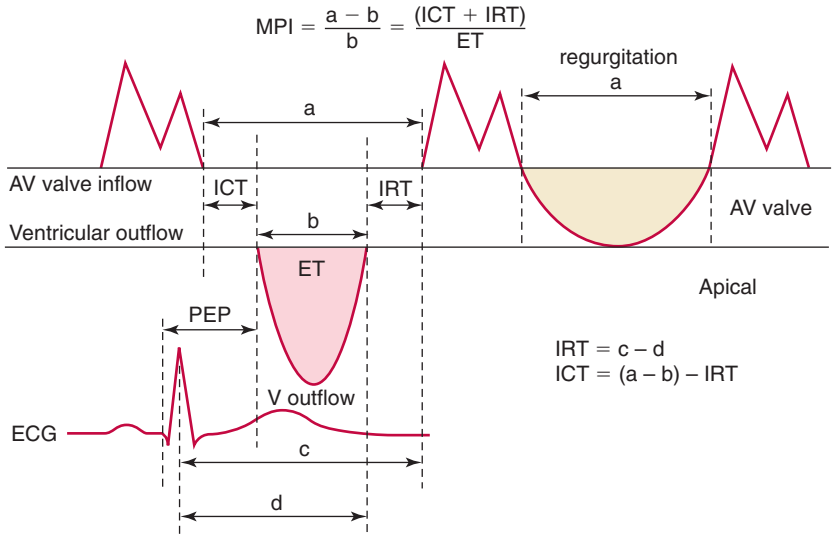

FIGURE 14–4 Doppler Tei index ([a – b]/b). Interval between end and onset of the atrioventricular (AV) inflow. Ejection time. Isovolumetric relaxation time (IRT) is the interval between the end of ventricular ejection and onset of AV inflow. Isovolumetric contraction time (ICT) is obtained by subtracting IRT from (a – b). AV, auriculo-ventricular; PEP, pulmonary ejection period.

their own performance with quantitative methods. All echocardiographic approaches for the assessment of regional and global ventricular function also need to take into account the quality of endocardial border definition, asynchronous contraction patterns observed with pacemakers or conduction defects, abnormal postoperative septal motion, and heterogeneity of normal ventricular function.

Tei[10] has described a Doppler-derived index combining systolic and diastolic time intervals called the myocardial performance index (MPI), or Tei index. This index is defined as the sum of isovolumic contraction and relaxation time divided by the ejection time (Fig. 14-4). In a multivariate analysis, Poulsen and associates[11] have found that an MPI of 0.60 in post-AMI patients was an independent predictor of heart failure or cardiac death. Similar findings and MPI cutoff values have been reported in AMI patients by others.[12]

The M-mode mitral annulus motion toward the apex also can be used as an indirect measure of left ventricular systolic function. It is usually measured in the apical four-chamber view, where the movement of the mitral annulus is parallel to the ultrasound beam and is normally 12 ± 2 mm. A motion of less than 8 mm has been reported to have a sensitivity of 98% and a specificity of 82% for the identification of an ejection fraction less than 50%.[13] Pai and coworkers have examined the mitral annular systolic excursion in 57 patients with a wide range of LVEFs (13% to 84%) and found a good correlation ($r = 0.95$; $P < 0.001$) with the ejection fraction measured by a radionuclide approach.[14] This method is seldom currently used, but may be helpful in patients with poor echogenicity. A modern version of this method relies on Doppler tissue imaging (DTI) of the mitral annulus and is discussed later in this chapter.

Quantitative Evaluation of Global Left Ventricular Systolic Function

Quantitative evaluation of global left ventricular systolic function is based on endocardial border tracing, with or without epicardial border tracing, at end-diastole and end-systole in one or preferably several views.[15-18] Assessment is based on analysis of wall motion (endocardial excursion) or wall thickening (interface separation). Evaluation of regional wall thickening is not influenced by cardiac translation or rotation, as opposed to wall motion, but requires excellent definition of the endocardial and epicardial borders, which constitutes its major limitation.

Quantitative assessment of global systolic function requires the determination of the LV cavity dimensions. Volume estimations are based on geometric assumptions about ventricular shape, which range from a simple ellipsoid to a complex hemicylindrical, hemiellipsoid shape. Descriptions of each geometric shape and the corresponding formula and requirements are beyond the scope of this chapter. The American Society of Echocardiography (ASE) recommendations for chamber quantification favors the modified Simpson's biplane method for LV volumes and ejection fraction.[19] The Simpson biplane method involves tracing of the endocardial borders in the apical four-chamber and two-chamber views, at end-systole and end-diastole. Determination of the LV end-diastolic volume (EDV) and end-systolic volume (ESV) allows calculation of the stroke volume (EDV – ESV = SV), cardiac output (SV × heart rate), and ejection fraction ([SV/EDV] × 100).[20]

Validation studies suggest that real-time three-dimensional echocardiography (3DE) is superior to standard two-dimensional echocardiography (2DE) in the determination of LV and right ventricular (RV) volumes and mass, using cardiac magnetic resonance imaging (MRI) as the gold standard.[21] In a study comparing 55 AMI patients with LVEF < 40%, 3DE-derived EDV, ESV, and ejection fraction (EF) had better correlation with MRI ($r = 0.96$; 95% CI, 0.93 to 0.97) than 2DE ($r = 0.88$; 95% CI, 0.84 to 0.92).[22]

Quantitative Evaluation of Regional Left Ventricular Systolic Function and Assessment of Myocardial Ischemia

Notable advances in recent years have been done in the field of quantitative evaluation of regional wall motion abnormalities. Tethering creates a movement distortion that renders qualitative or eyeball evaluation of regional LV dysfunction somewhat inaccurate. Reproducibility between physicians and different echocardiographic laboratories is not high in less experienced hands. A myriad of new technologies are being developed and it is beyond the scope of this chapter to consider all emerging methods. Here we will discuss the most commonly used approaches in clinical echocardiography laboratories.

Doppler Tissue Imaging. Myocardial DTI uses the pulsed Doppler method (modified to record the low-velocity, high-amplitude signals from tissue) to measure the velocity and timing of myocardial motion. Because Doppler signals are angle-dependent, the apical views are usually chosen. Different velocity profiles are obtained, called peak systolic (S_1m, S_2m), peak diastolic rapid filling (Em), and atrial contraction (Am). Although reasonably well correlated with global LV function, these measures are limited by preload and afterload dependence,[23] and are sensitive to inotropic stimulation and ischemia.[24] Furthermore, complete characterization of myocardial motion requires correction for radial, circumferential, and longitudinal movements, which is not currently being performed in clinical practice. Mitral annular sites are easy to identify, even in patients with poor imaging quality, so assessment of long-axis systolic function by DTI may enable estimation of the LVEF in these patients. Yuda and colleagues[25] have measured the peak systolic velocity of the septal, lateral, anterior, and inferior sites of the mitral annulus in patients with poor echogenicity. An averaged $S_m < 7.1$ cm/s in these patients has a sensitivity and specificity of 64% and 89%, respectively, for LVEF < 50%.

Strain and Strain Rate Imaging (SRI). The strain rate (SR) is defined as the difference in myocardial velocity between two axial points (usually 12 mm apart) along the path of the echocardiographic beam per unit time as measured by DTI; it reflects the speed of myocardial deformation. Strain (ε), is the integral of strain rate over time.[26] Two equations may be used to calculate strain and strain rate, as follows:

$$\varepsilon = \Delta L/\Delta L_0$$

and

$$SR = (\Delta L/\Delta L_0)/\Delta t = [v(I_0) - v(\Delta L + I_0)]/L_0$$

where ΔL is the change in length, Δt is the time required for the measured change in length, L_0 is the original length, and v is the measured velocity.

These measurements represent the instantaneous and total deformation of the myocardium within a region of interest (ROI), and provide additional information about L_0 and the nature and function of cardiac tissue. Whereas DTI reflects the movement of the ROI relative to the transducer, strain represents the movement of one tissue site relative to another within the ROI. This approach permits us to differentiate between movement caused by tethering of adjacent tissues and normal motion, which is crucial when dealing with CAD.

SRI can be used to assess myocardial ischemia. Seventeen patients undergoing coronary angioplasty were studied with DTI, SRI, and WMSI during and after left anterior descending coronary (LAD) balloon occlusion.[27] Strain decreased considerably in 94% of patients during occlusion, whereas peak systolic velocity by DTI decreased in only 65% of patients, suggesting a better sensitivity to ischemia for SRI than DTI alone.

Hence, DTI and SRI provide complementary information in CAD, the most interesting aspect of strain and strain rate being their independence from tethering. However, some technical issues need to be overcome before their widespread use can be recommended. First, misalignment between the ROI and transducer or inadequate signal-to-noise ratio (especially for SRI) may lead to false results; also, proper frame rate and pulse repetition frequency should be used. Lastly, off-line analysis could be time-consuming but, fortunately, most manufacturers have preprogrammed this technology in their recently developed machines. Another important issue is the lack of consensus regarding measurements, recommended segments to be analyzed, and their optimal cutoff values.

Contrast Echocardiography: Left Ventricular Opacification and Blood Flow Assessment

Despite improved ultrasound imaging, up to 10% to 20 % of patients have suboptimal endocardial border definition to allow for quantitative assessment of LVEF.[28] Contrast echocardiography can be used to improve the delineation of the endocardial borders. The contrast agents used are lipid-shelled, gas-filled encapsulated microbubbles. They have been extensively used and are clinically available in most echocardiographic laboratories for left ventricular cavity opacification (LVO). LVO can also be useful for the diagnosis of mural thrombus or left ventricular aneurysm. In the ACS setting, LVO offers the advantage of better assessment of LV regional wall motion abnormalities by increasing the number of interpretable segments.[29]

Quantification of myocardial blood flow can also be obtained using myocardial contrast echocardiography (MCE). Microbubbles are infused at a steady state and their concentration within the myocardial tissue will remain constant because the number of microbubbles entering a microcirculatory bed will equal the number leaving it. High-power ultrasound waves destroy microbubbles at regular intervals and determination of their replenishment rate between destructive beam pulses will reflect the rate of blood transiting through the tissue. Myocardial blood volume and velocity can then be determined after mathematical transformation.[30]

MCE provides short- and long-term prognostic information in addition to clinical (TIMI risk score), standard echocardiographic, and serologic markers in the evaluation of chest pain in the emergency department.[31] MCE can also be useful in the evaluation of the success of reperfusion after pharmacologic or mechanical revascularization, in addition to the classic clinical and electrocardiographic parameters. This approach can indeed allow detection of the so-called no-reflow phenomenon.[32-34] In addition, the use of MCE has been proposed to assess myocardial viability and predict late functional recovery after AMI.[35]

Evaluation of Diastolic Function in Acute Coronary Syndromes

Studies have shown changes in the transmitral flow profile after balloon inflation-induced coronary occlusion, which are secondary to impaired left ventricular relaxation.[36] There is a decrease in the peak rate of early filling (E wave), resulting in a reduced proportion of total left ventricular filling during the rapid filling phase, an increased rate of filling secondary to atrial contraction (A wave), and a reduced E/A ratio with a prolonged deceleration time (Fig. 14-5).[37] These changes parallel the worsening of diastolic function measured invasively by the peak negative dP/dt, left ventricular end-diastolic pressure, and time constant of isovolumic relaxation (tau), and may be present even when systolic function remains normal.[38] In ACS, most patients present with the typical abnormal relaxation pattern (E/A ratio < 1, prolonged mitral deceleration time >50 msec). A large infarct size or severe systolic dysfunction can result, however, in a restrictive pattern (high peak E wave velocity, E/A > 2, and deceleration time <150 msec), which reflects abnormal ventricular compliance with elevated filling pressures.[37] A third intermediate or pseudonormal Doppler pattern also can be seen, with the E/A ratio between 1 and 2 and a deceleration time between 150 and 250 msec. According to some authors, the Valsalva maneuver can be used to unmask this pattern, because the decrease in venous return will reveal abnormalities in the mitral E/A ratio (<1) and deceleration time (>250 msec) in patients with the pseudonormal pattern, but these indices

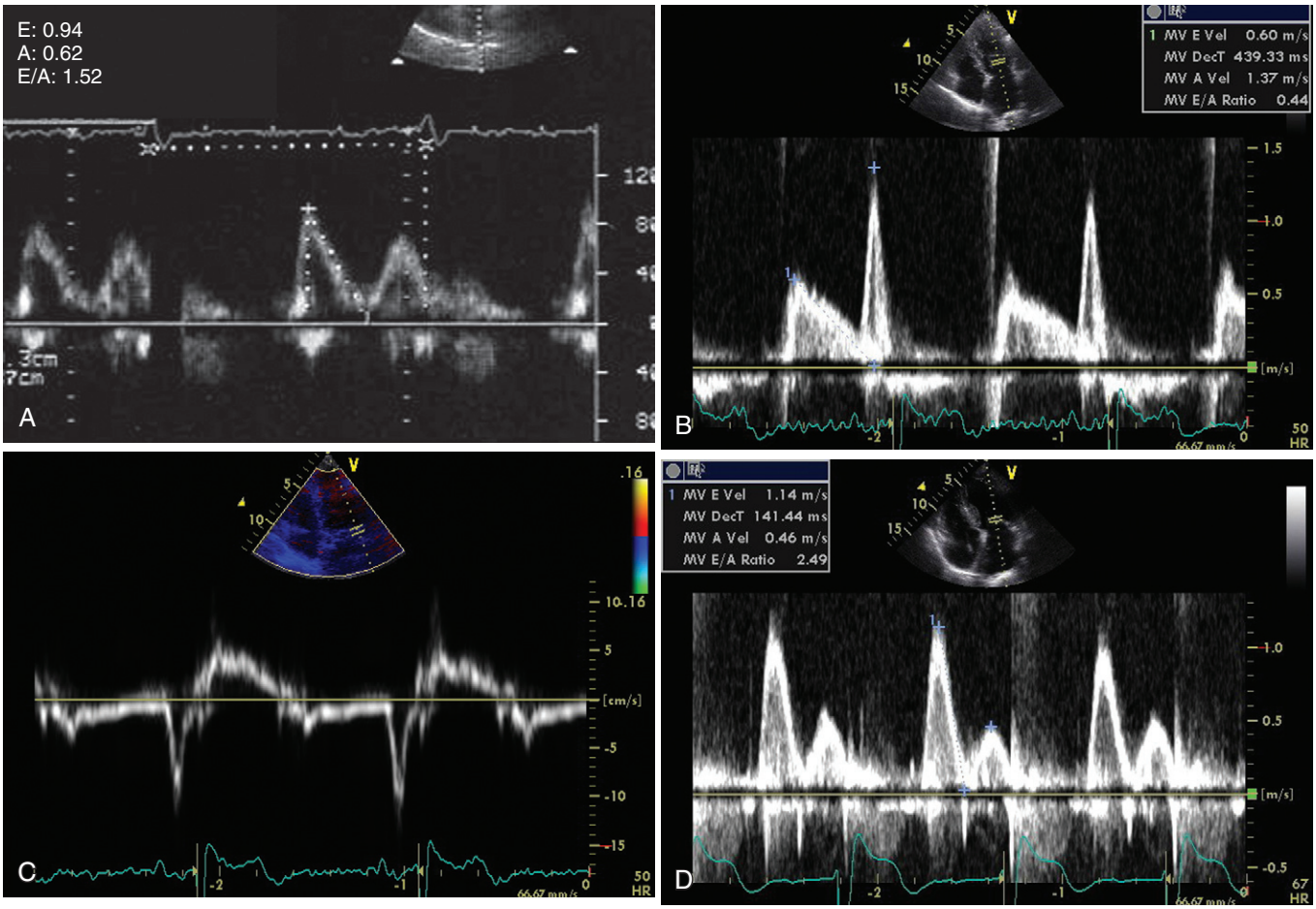

FIGURE 14–5 **A**, Example of a normal Doppler mitral profile. The E wave is 94 cm/sec, deceleration time (DT) is 174 msec, and E/A ratio is 1.0. **B,** Mitral flow velocity recording shows abnormal relaxation. The E/A ratio is 0.44 and DT is prolonged (439 msec). **C,** DTI of the mitral annulus at the lateral level, depicting inversion of the normal pattern, with E′ < A′. **D,** Restrictive mitral valve flow pattern with short DT (141 msec) and E/A of 2.5.

will remain normal in patients without diastolic dysfunction.[39,40] This pseudonormal pattern can also be differentiated from a truly normal Doppler profile by determining the isovolumic relaxation time using the mitral and aortic Doppler profiles, analyzing the DTI pattern at the mitral annulus (inverted E to A ratio), or examining pulmonary venous flow.[37]

DTI is useful in the assessment of diastolic function. The pattern of mitral annulus motion during diastole is similar to that of the pulsed-wave Doppler (PWD) transmitral flow but lower in velocity. From mitral annulus velocity Doppler signals, early diastolic (E_m), atrial contraction (A_m), and E_m/A_m ratio can be derived. Being less dependent on preload than the PWD transmitral profile, the E_m/A_m pattern on DTI helps distinguish normal left ventricular filling from the pseudonormal pattern seen in patients with moderate to severe diastolic dysfunction.

In experimental models, restoration of normal coronary flow causes the Doppler changes to return to baseline within 15 seconds. Normalization of the Doppler velocity profile can be delayed, however, in the clinical setting. After successful coronary angioplasty, improvement in the transmitral flow velocity profile may take 48 hours or sometimes several days, depending on the duration and severity of the ischemic insult before revascularization.[41,42] This delayed normalization may reflect improvement in diastolic function of the myocardial segments that previously were chronically ischemic or stunned.

ROLE OF ECHOCARDIOGRAPHY IN THE EMERGENCY DEPARTMENT

Patients with chest pain in the emergency department (ED) can present an important diagnostic dilemma. Chest pain may be the manifestation of several cardiac and noncardiac disorders, one of the most important being AMI. The early treatment of AMI is crucial to improve myocardial perfusion, limit cell necrosis, and ultimately save the patient's life. Because early treatment leads to better results, a method that accurately and rapidly diagnoses these patients is of great clinical utility. Usually, the diagnosis of AMI is based on the triad of the clinical history, ECG, and serum enzyme levels. The clinical history is frequently neither classic nor specific. Levels of cardiac enzymes are often normal on initial sampling and can take many hours to become elevated.[43] A typical injury pattern on the ECG is helpful when present but provides a specific diagnosis in only 40% to 50% of patients with ACS.[44] This problem is particularly evident in patients with an occlusion of the circumflex artery.

The early diagnosis of AMI from this classic triad is not always possible. Fewer than one third of patients presenting to the ED with chest pain are eventually proved to have ACS, whereas 5% to 10% of patients who do have AMI are mistakenly discharged from the ED.[45,46] The accurate distinction between the two groups of patients is challenging and important. Alternate diagnostic strategies have been suggested and include serial enzyme assessment, ST-segment monitoring,

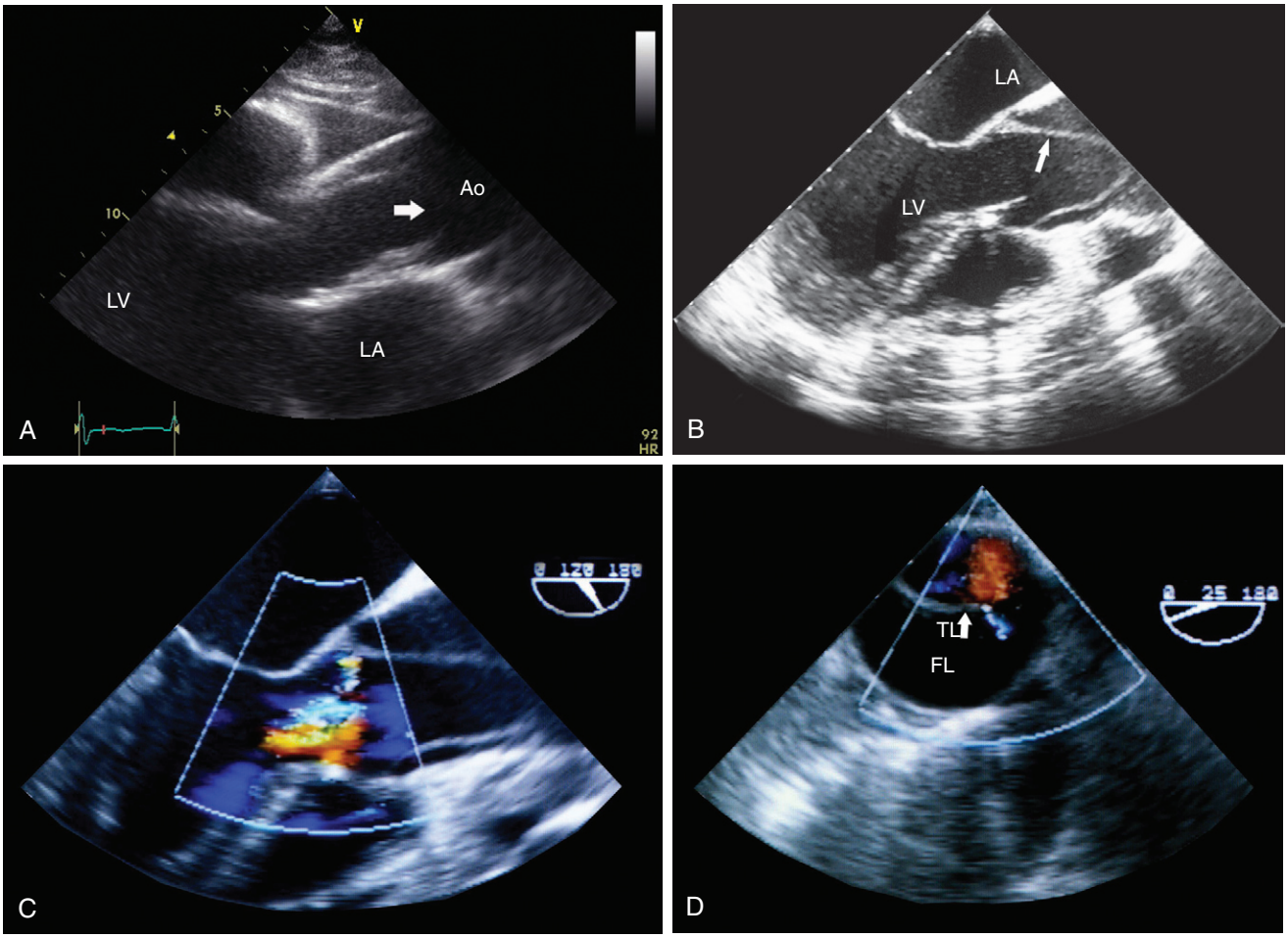

FIGURE 14–6 **A,** Transthoracic echocardiography shows a typical dissection of the ascending aorta, observed in the parasternal long-axis view, with the intimal flap (*arrow*) identified. **B,** Transesophageal echocardiography at the midesophageal level in the long-axis view (120 degrees) depicting the aortic dissection. **C,** Color flow Doppler revealed the associated aortic regurgitation. **D,** Short-axis view of the descending thoracic aorta shows communication between the true lumen (TL) and false lumen (FL), which are separated by the intimal flap (*arrow*). LA, left atrium; LV, left ventricle.

and early exercise testing. Because echocardiography allows rapid bedside assessment, it may be the optimal method for early diagnosis of acute ischemia and AMI in patients with suggestive symptoms but nondiagnostic ECGs.[47] The presence of a regional wall motion abnormality on echocardiography has a high sensitivity (88% to 93%) but relatively low specificity (41% to 53%) for the diagnosis of AMI.[48-50] The absence of such wall motion abnormalities during or immediately after chest pain identifies a subset of patients, however, unlikely to have an AMI, with a negative predictive value of approximately 98%.[51] Kontos and associates have compared two-dimensional echocardiography and radionuclide scintigraphy, with a concordance of 89% between both modalities.[52] Some clinical centers use exercise echocardiography after normal standard echocardiography to evaluate patients with suspected myocardial ischemia in the ED to allow an early discharge.[53]

Echocardiography can be a useful tool in the emergency department for the triage of chest pain. It can help for the diagnosis of ACS, evaluation of the myocardial area at risk and of global ventricular function, and rapid and precise identification of complications in unstable patients. Echocardiography can also be useful in excluding other possible causes of chest pain, such as aortic dissection (Fig. 14-6), massive pulmonary embolus (Fig. 14-7), acute pericarditis

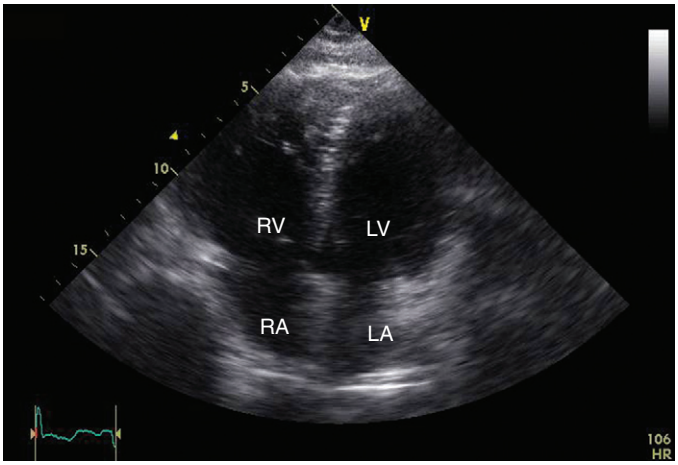

FIGURE 14–7 Apical four-chamber view shows severely dilated RV (in a patient presenting to the emergency ED with atypical chest pain and tachycardia 10 days after a long automobile trip), secondary to pulmonary embolism and severe pulmonary hypertension. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

with pericardial effusion, aortic stenosis, hypertrophic cardiomyopathy, and mitral valve prolapse. In addition, echocardiography can provide important prognostic information about patients with chest pain by identifying patients at risk of early or late cardiac events, in addition to clinical and electrocardiographic variables.[54] The incidence of these cardiac events (death, urgent revascularization, AMI) is increased significantly in patients with chest pain, wall motion abnormalities, and impaired systolic function compared with patients without left ventricular dysfunction on echocardiography.[55]

The 2003 College of Cardiology (ACC), American Heart Association (AHA), and American Society of Echocardiography (ASE) guidelines[56] for the clinical application of echocardiography suggest that the following objectives represent class I indications in patients with chest pain:

- Diagnosis of underlying cardiac disease in patients with chest pain and clinical evidence of valvular, pericardial, or primary myocardial disease
- Evaluation of chest pain in patients with suspected acute myocardial ischemia, when baseline ECG and other laboratory markers are nondiagnostic and when the study can be obtained during pain or within minutes after its abatement
- Evaluation of chest pain in patients with suspected aortic dissection
- Evaluation of patients with chest pain and hemodynamic instability unresponsive to simple therapeutic measures
- Triage of patients with chest pain in the emergency department

ECHOCARDIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

Using correlative studies with coronary angiography and echocardiography in patients with AMI, the specific coronary artery perfusing each left ventricular segment was determined (Fig. 14-8). In the parasternal long-axis view, the anterior interventricular septum is perfused by the left anterior descending artery, the first 1 to 2 cm being perfused by the first septal perforator, allowing determination of whether the obstruction is proximal or distal to this left anterior descending branch. The inferolateral wall usually is perfused by the circumflex artery. In the parasternal short-axis view, the left anterior descending artery supplies the anterior wall and anterior septum, the circumflex artery supplies the lateral wall, and the right coronary artery supplies the inferior septum and inferior wall. In the apical two-chamber view, the anterior wall is perfused by the left anterior descending artery, the inferior wall is supplied by the right coronary artery, and the apex often has a dual coronary supply. In the apical four-chamber view, the midseptum is perfused by the left anterior descending artery, the basal septum is usually part of the right coronary artery territory, the apex is usually perfused by the left anterior descending artery, and the basal and midlateral walls are supplied by the circumflex artery.

The early stage of a nonrevascularized transmural AMI is characterized on echocardiography by decreased amplitude of regional endocardial excursion with normal wall thickness, followed in 4 to 6 weeks by wall thinning in the affected region and often increased echogenicity secondary to a fibrotic response. A transmural infarction generally produces profound changes in regional left ventricular function, with most of the affected segments being akinetic or dyskinetic and the others being severely hypokinetic. In contrast, a nontransmural infarction results in a lesser degree of hypokinesis and better global ventricular function.[57,58] Studies have found a good correlation between histologic evidence of infarction

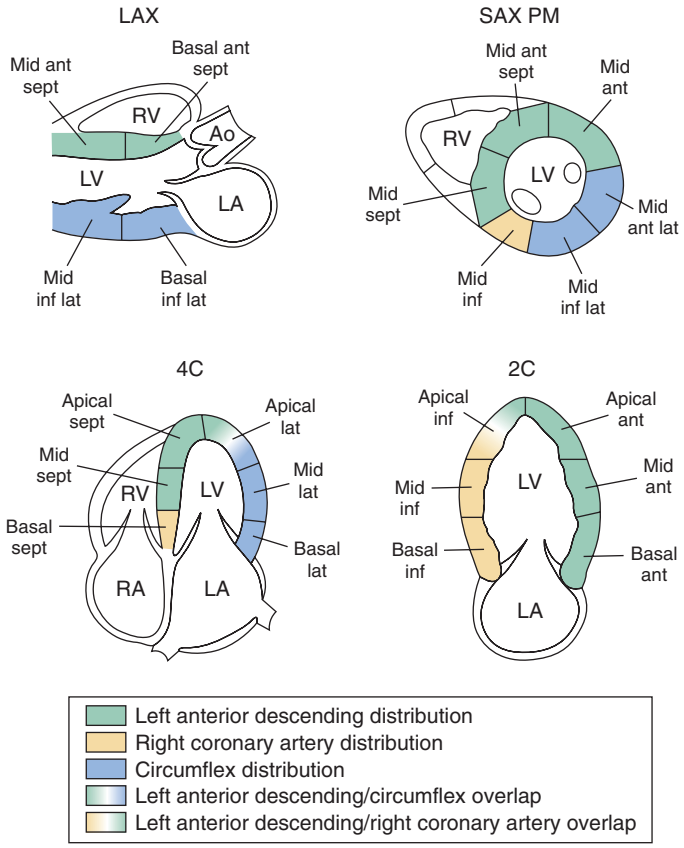

FIGURE 14–8 Diagram shows coronary perfusion of the 16 left ventricular segments. The apical lateral segment may be supplied by the left anterior descending artery or the circumflex artery. The apical inferior segment may be supplied by the left anterior descending artery or the right coronary artery. 2C, apical two-chamber view; 4C, apical four-chamber view; LAX, parasternal long-axis view; SAX PM, parasternal short-axis view at the papillary muscle level.

and the presence of segmental dysfunction on echocardiography in more than 90% of cases.[59] Experimentally, necrosis of 20% or less of the wall thickness results in a decrease in systolic thickening of approximately 50%, whereas necrosis of more than 20% of the thickness of the myocardium is uniformly associated with systolic thinning.[60,61] The presence or absence of wall motion abnormalities may be related more to the extent of transmural involvement than to the circumferential extent of an infarct.[62] Shortly after coronary occlusion (<2 days), experimental and clinical studies also have shown that the extent of wall motion abnormalities as shown by echocardiography correlates well with actual infarct size.[63] Echocardiography can overestimate infarct size, however, because of contractile abnormalities (tethering) in the noninfarcted myocardium immediately adjacent to the severely ischemic regions.[59,61] The mechanism responsible for the phenomenon may be that the vulnerable myocardium is metabolically abnormal (adenosine triphosphate depletion) and is placed under unfavorable regional loading conditions, leading to apparent dysfunction.[64]

Relationship Between Abnormal Wall Motion and Electrocardiographic Infarct Location

Heger and associates[3] have reported that 95% of patients with electrocardiographic evidence of Q waves in leads II, III, and aVF have wall motion abnormalities involving at least one of

the inferior segments. When the inferior wall myocardial infarction was complicated by a ventricular septal defect, echocardiography identified involvement of the inferior portion of the interventricular septum despite the absence of electrocardiographic evidence of septal involvement in these patients.[3] The echocardiographically defined wall motion abnormalities were a better predictor of the extent and location of infarction, especially because the inferior septum cannot be assessed accurately by the ECG. Lateral wall involvement often is associated with inferoposterior infarction. Patients with inferoposterior infarction and lateral wall involvement on the ECG have wall motion abnormalities that usually extend to the basal segments.[66] When an anterior wall infarction is identified on the ECG, at least one of the anterior segments presents a regional wall motion abnormality on echocardiography.[3] The extent of wall motion abnormalities is influenced by the location of the obstruction in the left anterior descending coronary artery.[67] All the segments of the anterior septum, anterior wall, and apex are affected if the obstruction occurs proximal to the first septal perforator artery, whereas obstruction distal to the first septal perforator characteristically spares the basal segments of the anterior septum and anterior wall. The sensitivity and specificity of the 12-lead ECG for the detection of an apical infarction are low, despite several electrocardiographic criteria.[68,69] In contrast, apical dysfunction is identified and quantified clearly by echocardiography, especially with LV opacification. One potential pitfall of transthoracic imaging is incorrect positioning in the apical views, which truncates the true left ventricular apex, but the experienced echocardiographer ensures that the transducer is sufficiently low and lateral on the chest to avoid this problem. No Q waves were found on the ECG in more than one third of 64 patients with apical akinesis by echocardiography.[70] When abnormal Q waves were present and apical asynergy was identified by echocardiography, the ECG correctly localized the infarct at the apex in only 10% of patients.[70] Nevertheless, the presence of Q waves is associated with a larger area and more severe degree of apical dysfunction, and persistent ST-segment elevation may suggest the presence of a left ventricular aneurysm on the echocardiogram.

Echocardiography After Reperfusion Therapy

Multiple prospective randomized trials have shown that the restoration of antegrade flow after pharmacologic or mechanical reperfusion is usually associated with improved wall motion, fewer complications, and decreased mortality. The extent of systolic function recovery is related to the duration of the occlusion (a prompt treatment begun in the first 2 hours after the onset of the chest pain gives the best results), extent of the ischemic zone, and success of reperfusion.[2] The time to complete functional recovery after reperfusion varies from patient to patient and from segment to segment in the same patient. Studies with sequential echocardiograms suggest, however, that recovery usually occurs 24 hours to 10 days after reperfusion but may take 3 to 4 weeks if stunning is present.[71] The stunned myocardium has had, by definition, flow restored (by angioplasty, thrombolysis, or spontaneously), yet remains temporarily dysfunctional. Echocardiography combined with dobutamine infusion (5 to 10 μg/kg/min) can be used to distinguish stunned myocardium after thrombolytic therapy from nonviable myocardium, with the former responding to low-dose inotropic stimulation.[65] The value of contrast echocardiography to determine microvascular integrity and myocardial reperfusion has been discussed earlier.

The role of echocardiography in the assessment of left ventricular remodeling goes beyond the short-term evaluation during the course of an ACS. In successfully reperfused patients, left ventricular dimensions remain stable and tend to regress 3 months after AMI, whereas left ventricular dimensions continue to increase in patients without successful reperfusion.[72] Late reperfusion with thrombolytic therapy may prevent acute and chronic infarct expansion, regardless of myocardial salvage.[73,74] Patency of the infarct-related coronary artery (by spontaneous reperfusion or by angioplasty), occurring within days of the AMI, also has been associated with an improvement in regional function and an attenuation of the left ventricular dilation 1 to 6 months after the initial event.[75,76]

Complications of Myocardial Infarction

Echocardiography is a sensitive, rapid, and useful tool for the diagnosis of complications after AMI. In the few cases in which the transthoracic approach, even with contrast, does not allow adequate assessment, transesophageal echocardiography (TEE) can lead to the correct diagnosis or to a more precise evaluation of the complication.

Left Ventricular Aneurysm

Most left ventricular aneurysms are complications of AMI and are classified as true or false aneurysms.

True Aneurysm. This is the most common type of ventricular aneurysm, which occurred in approximately one fifth of all cases of transmural AMI before the routine use of reperfusion therapy. In 1986, in a prospective echocardiographic study, Visser and coworkers reported that a left ventricular aneurysm was found in 22% of nonreperfused transmural MI patients, 32% and 9% of anterior and posterior infarcts, respectively.[77] The aneurysm results from expansion of the infarct area and thinning of the myocardium and contains all three layers of the ventricular wall. Echocardiographically, the aneurysmal segments are dyskinetic or akinetic and cause distortion of the left ventricular shape (with a wide neck), which persists in diastole. Almost 90% of true left ventricular aneurysms involve the apex, but extension to the anterior wall is common. The remaining cases generally involve the inferobasal region. Detection of an aneurysm within the first 5 days of hospitalization has been associated with high mortality rates at 3 months and 1 year after MI, probably reflecting the larger infarct size and the more depressed global systolic function.[77,78] Aneurysm can also be a site of predilection for thrombus formation.

False Aneurysm or Pseudoaneurysm. This rare and potentially life-threatening entity results from a rupture through the myocardium, with the extravasated blood being contained by the parietal pericardium. Pathologically, a small channel connects the left ventricle with a large blood- and thrombus-filled cavity lined by fibrous pericardial tissue, and a tear in the myocardium can be identified. Echocardiographically, an echo-free area outside the left ventricular cavity is seen connected to it by a narrow neck, with an abrupt interruption in the ventricular wall. Bulging can also be observed in the false aneurysm during each systole (Fig. 14-9).[79] Because a ventricular pseudoaneurysm is a contained rupture, mortality is high and urgent surgery is warranted as soon as the diagnosis is made with echocardiography.

Ventricular Septal Defect

A ventricular septal defect (VSD) is an uncommon complication of AMI (<1%) associated with high mortality rates of 54% in the first week and 87% within 2 months if left untreated.[80] Most ischemic ventricular septal defects are associated with extensive MI and multivessel CAD. Rupture of the interventricular septum is more common with anterior than inferior infarcts. The perforation may be a direct through-and-through hole or may be more irregular and serpiginous

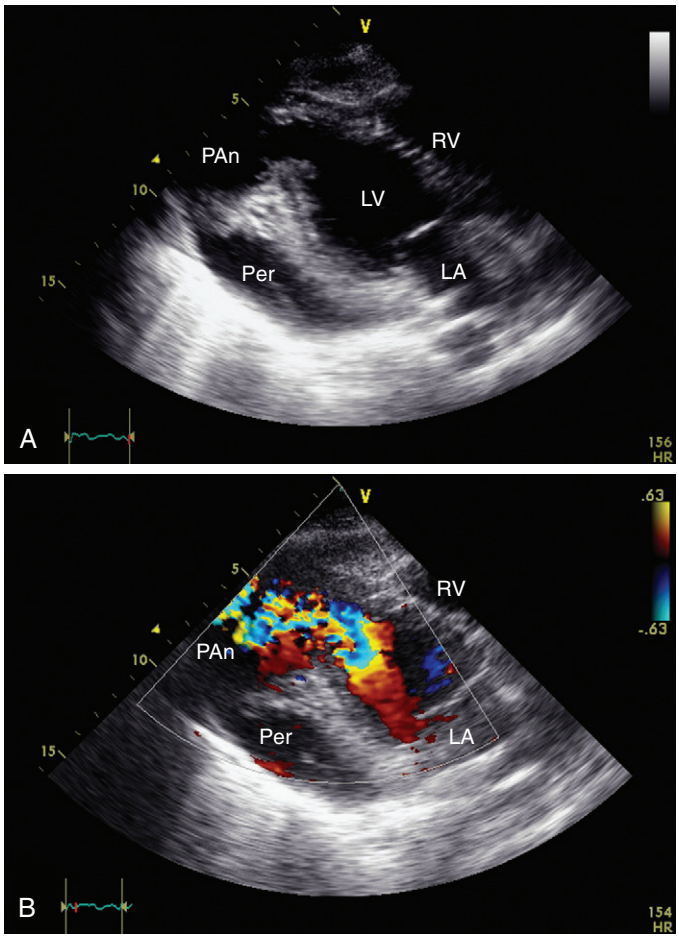

FIGURE 14–9 A, Apical long-axis view, slightly off-axis, shows abrupt discontinuity of the distal inferolateral wall, resulting in a communication between the LV and a large cavity that appears to be a pseudoaneurysm. The "aneurysmal" cavity was pulsatile during real-time imaging. **B,** On color Doppler, flow is seen from the LV toward the pseudoaneurysmal cavity (*arrow*). LA, left atrium; LV, left ventricle; PAn, pseudoaneurysm; Per, pericardial effusion; RV, right ventricle.

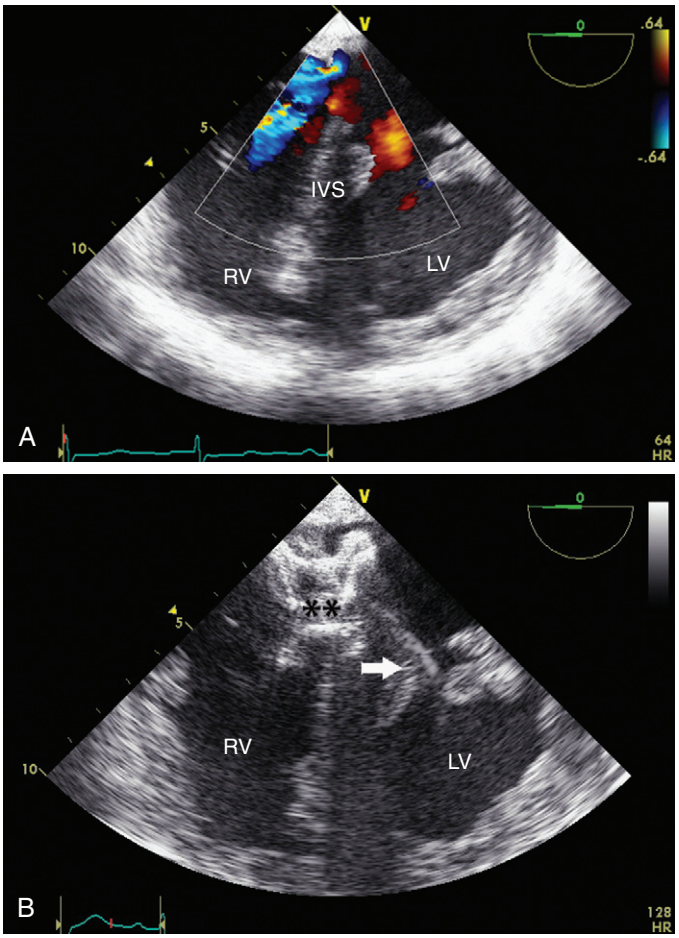

FIGURE 14–10 Three days after an acute inferior myocardial infarction, clinical deterioration and a new systolic murmur were observed in this patient. **A,** Transesophageal transgastric view at 0 degree with color Doppler showed a shunt from the left to the right ventricle, typical of a ventricular septal defect (VSD). **B,** TEE guidance of percutaneous closure of this VSD. IVS, interventricular septum; LV, left ventricle; RV, right ventricle; *arrow*, delivering catheter; **, Amplatzer device.

with a variable defect size, but usually less than 4 cm in diameter. The time from the onset of pain until septal perforation can vary from a few hours to 9 days after AMI but is on average 3 to 4 days. Echocardiography often detects the septal defect directly as an interruption in the myocardium in an akinetic region, often at the junction with normal or hyperkinetic tissue (Fig. 14-10). Kishon and colleagues have reported that 2DE identified 68% of ventricular septal defects after MI, but the sensitivity was increased to 95% when two-dimensional imaging was combined with Doppler evaluation.[81]

As a complication of anterior infarction, the septal defect usually is located distally near the apex, in association with anterior akinesis. Careful two-dimensional and color Doppler scanning of the ventricular septum is required during the echocardiographic examination, particularly in the apical four-chamber and five-chamber views. When a VSD occurs with an inferior infarction, the apex generally is spared and the defect is in the basal septum, generally associated with an extensive area of inferior wall dyskinesis. Commonly, the VSD in the basal inferior septum is identified using an off-axis position, with an intermediate rotation between the apical four-chamber and two-chamber views. Pulsed, continuous-wave, and color Doppler confirm the left-to-right shunt across the septal defect. The defect size determined by color Doppler echocardiography has been shown to correlate closely with that determined at surgery or autopsy and with the pulmonic-to-systemic flow ratio measured at cardiac catheterization.[82] In addition, transesophageal echocardiography (TEE) is useful in guiding percutaneous VSD closure (see Fig. 14-10B).

Papillary Muscle Rupture

Papillary muscle rupture is a rare but dramatic complication of an acute transmural MI. Because its blood supply is dependent on a single coronary artery, the posteromedial papillary muscle is more frequently affected. For that reason, papillary muscle rupture occurs more commonly in the setting of an inferior wall MI. Clinically, partial rupture of a papillary muscle head is seen more frequently, because complete rupture generally is rapidly fatal. 2DE can show the structural abnormality of the mitral apparatus accurately, which usually includes a flail leaflet or prolapse and partial or complete rupture of one of the papillary muscle heads, and also allows exclusion of the presence of a VSD (Fig. 14-11).[83] Because chordae tendineae originating from the posteromedial papillary muscle are connected to both mitral leaflets, it is important to realize that a flail anterior leaflet can complicate an acute inferior wall infarct. The left ventricle is often hyperdynamic in the presence of papillary muscle rupture, and this frequently renders the identification of a regional wall motion abnormality in the inferior wall difficult. The addition of

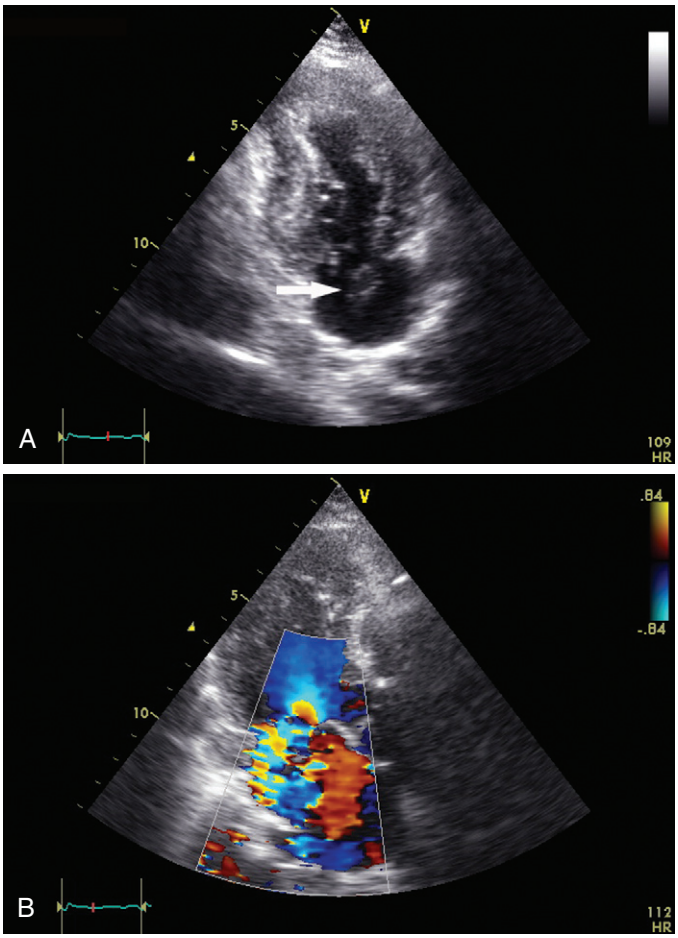

FIGURE 14–11 Transthoracic echocardiography in a patient in cardiogenic shock 24 hours after an anterior non–ST-segment elevation myocardial infarction (NSTEMI). **A,** Apical two-chamber view shows rupture of the anterolateral papillary muscle, which moved freely into the left atrium (*arrow*). **B,** Apical long-axis view shows severe mitral regurgitation in the same patient.

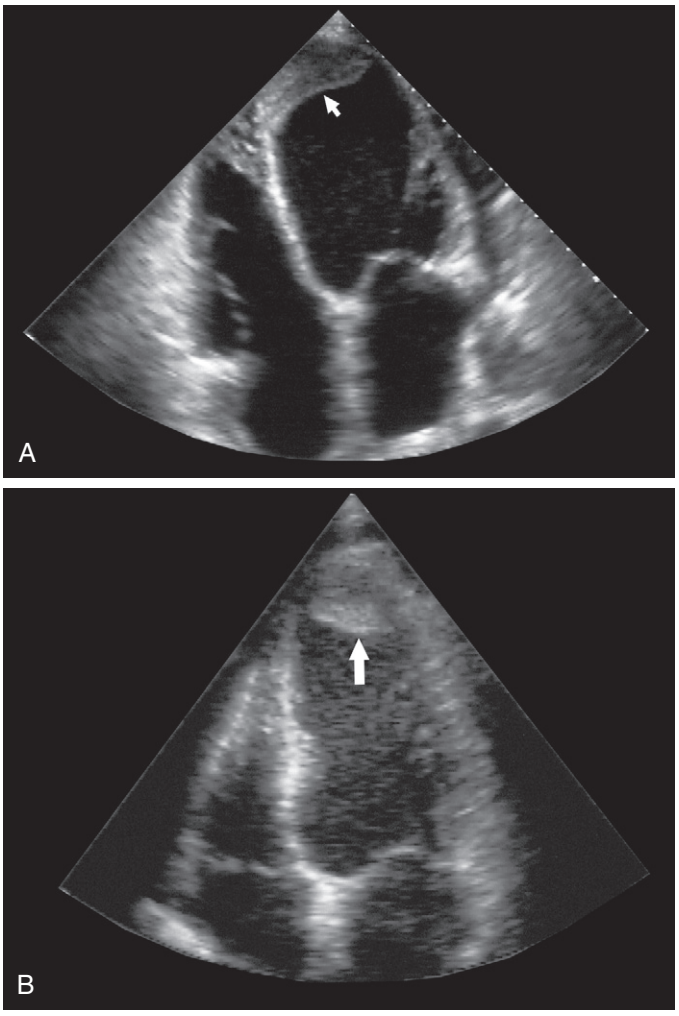

FIGURE 14–12 **A, B,** Left ventricular thrombi in the apical four-chamber view from two different patients. An organized and nonmobile thrombus is detected in the first patient (*arrow* in **A**), and a mobile thrombus (*arrow* in **B**) is seen in the second patient in a region of akinesia and apical aneurysm. The latter patient suffered a stroke within hours of this echocardiographic examination.

color flow Doppler permits the identification of mitral regurgitation and assessment of its severity in almost all patients, with excellent correlation with angiography.[84] In the presence of an eccentric jet or noncompliant left atrium (as commonly encountered in this setting), color Doppler occasionally may underestimate the severity of mitral regurgitation, however, and a thorough echocardiographic assessment is required, using TEE when needed.

Ventricular Free Wall Rupture

Rupture of the left ventricular free wall is usually a sudden event, which accounts for 10% to 15% of all in-hospital deaths after AMI, generally in older hypertensive patients with Q-wave infarcts. Impending cardiac rupture may be suspected in the setting of post-MI pericarditis, repetitive emesis, restlessness, and agitation or if there is a deviation from the expected pattern of T-wave evolution on ECG.[85] Echocardiographic recognition of free wall rupture, although unusual because of rapid hemodynamic deterioration, occasionally has been shown, allowing rapid intervention.[85]

Left Ventricular Thrombus

A relatively frequent complication of AMI before the era of thrombolytic therapy, LV thrombi are found more often after anterior wall and large infarcts, as is the case for ventricular aneurysms.[86] Echocardiographically, a left ventricular thrombus appears as a focal mass on the endocardial contour of an akinetic or dyskinetic segment. It may be fixed, pedunculated, and freely mobile, or may have a fixed base, with mobile filaments extending from its surface (Fig. 14-12). A newly formed ventricular thrombus is often only mildly echogenic, but its appearance may be speckled or contain areas brighter than the surrounding myocardium. The echogenicity can increase, however, and calcification may be found when the thrombus is organized. Because most left ventricular thrombi are in the apical region, standard and off-axis apical views (with optimized imaging of the region of interest) often are required to confirm their presence and distinguish them from a near-field artifact or a fibrous band (false tendon). LV opacification with contrast agents may be useful in this situation. Before thrombolysis and routine anticoagulation of the high-risk patients, LV apical thrombi generally became echocardiographically detectable 5 to 10 days after MI. Echocardiographic detection of a left ventricular thrombus within 48 to 72 hours after an AMI has been reported to be associated with a poor prognosis, probably because it indicates extensive regional dysfunction.[87] Several prospective studies have reported that thrombi that are mobile, protrude into the ventricular cavity, or are adjacent to zones of hyperkinetic wall motion are more likely to result in an embolic event.[87,88] The natural course of left ventricular thrombi is variable; in several series, little change took place

in the first few months after AMI, although regression and ultimate disappearance are also possible.[88]

Right Ventricular Infarction

The clinical diagnosis of an RV infarction requires a high level of suspicion because the sensitivity and specificity of clinical and electrocardiographic signs are low.[89] Diagnosis of right-sided involvement in the setting of an acute inferior infarct can change the clinical management of these patients significantly, because intractable cardiogenic shock may become easily reversible with fluid infusion. Transthoracic echocardiography is an excellent modality to identify RV infarction. Two-dimensional echocardiographic findings include RV regional hypokinesis or akinesis or global dysfunction, usually with LV inferior wall involvement. Because infarction of the RV sometimes may be revealed only by dysfunction of its inferior wall, attention should be paid to this region in optimized parasternal short-axis views. RV dilation, tricuspid regurgitation, reduced excursion of the tricuspid annulus, and dilatation of the inferior vena cava can also be found and point toward the correct diagnosis.

The right ventricle has a complex crescent-shaped geometry; therefore, many methods for qualitative estimation of RVEF have been proposed. M-mode displacement of the RV base during systole and diastole in an apical four-chamber view, also called TAPSE (***t***ricuspid ***a***nnular ***p***lane ***s***ystolic ***e***xcursion), is an indirect measurement of RVEF. When compared against the more cumbersome but quantitative biplane Simpson method, an excursion of less than 1.5 cm has a 59% sensitivity and 94% specificity for the detection of RVEF of less than 50%.[90] An MPI or Tei index was also described for patients with RV infarction, with a value of 0.30 resulting in the best combination of sensitivity and specificity for the diagnosis of RV infarction in the context of LV inferior wall infarction.[91] Miller and associates[90] have also assessed DTI of the basal RV segments and MPI for the detection of RVEF less than 50%. Sensitivity and specificity of DTI less than 10 cm/sec were 59% and 92% and those of MPI more than 0.40 were 100% and 35%, respectively. MPI appears to be less specific, given the fact that it combines assessment of both systolic and diastolic function. Many studies have compared echocardiographic methods with radionuclide ventriculography as a gold standard.[92] A TAPSE less than 1.5 cm and DTI less than 12 cm/sec had good correlation with the RVEF, as assessed by the radionuclide technique, with sensitivity and specificity for predicting a RVEF less than 45% of 80% and 75% for M mode and 90% and 85% for DTI, respectively. Another method that has been proposed for estimating RVEF applies the Simpson rule from two orthogonal views using apical and subcostal windows. Although appealing, this method has poor reproducibility; correlation with MRI is low and is seldom used in practice. Finally, 3D echocardiographic estimates of RV size and RVEF show only moderate correlation to MRI measurements of these parameters, and are not better than simple 2D echocardiographic estimates of RV size and function. Hence, clinically TAPSE may be the preferred approach.[93] Strain and strain rate have also been proposed, with lower values in RV basal and midsegments in patients with LV inferior AMI with RV involvement than in patients without RV dysfunction.[94]

The adverse impact of RV dysfunction on major complications and mortality in patients with AMI was recognized several decades ago. A meta-analysis of six studies involving 1198 patients with inferior wall infarction compared patients with associated RV dysfunction to those without.[95] Patients with RV involvement were at significantly increased risk of death (odds ratio [OR], 3.2; 95% CI, 2.4 to 4.1), cardiogenic shock (OR, 3.2; 95% CI, 2.4 to 4.3), sustained ventricular tachycardia/ventricular fibrillation, VT/VF (OR, 2.7; 95% CI, 2.1 to 3.5) and advanced atrioventricular block (OR, 3.4; 95% CI, 2.7 to 4.2). Recently, Assali and coworkers[96] have confirmed these data in a modern cohort of 666 patients with AMI treated with a glycoprotein (GP) IIb/IIIa inhibitor, aspirin, and clopidogrel, and undergoing primary percutaneous coronary intervention (PCI). Procedural success was obtained in 95% of patients. Once again, RV involvement was associated with increased 30-day mortality (OR, 5.2; 95% CI, 1.6 to 17; $P = .005$). Furthermore, complete revascularization of the right coronary artery, including the major RV branch, was associated with a higher rate of RV function recovery by echocardiography and improved 30-day mortality (OR, 0.4; 95% CI, 0.1 to 1.05; $P = .06$). In the GISSI-3 echocardiography substudy, TAPSE was reduced in patients showing RV dysfunction,[97] but improved progressively after revascularization within 48 hours after MI and up to 6 months, suggesting that RV functional improvement occurs early after revascularized AMI.

Prognosis After Myocardial Infarction

The prognosis after MI is determined in part by the severity of systolic dysfunction (infarct size) and the presence and extent of ischemic myocardium.[98] In multivariate analyses, the WMSI has been found to be a stronger predictor of outcomes than most clinical and hemodynamic parameters.[6-8,99,100] A high WMSI value identifies patients at risk for in-hospital mortality, heart failure, malignant arrhythmias, and cardiogenic shock.[49] Sabia and colleagues[49] have reported that all patients with in-hospital complications (e.g., cardiogenic shock, life-threatening arrhythmias, recurrent angina) had regional wall motion abnormalities on their initial echocardiogram. The echocardiographic assessment of LVEF also predicts long-term prognosis after the infarct. In a study of 512 post-AMI patients followed with echocardiograms at 11 days and 1 year, the LV end-systolic area and systolic function were strong predictors of death and cardiac events, and prevention of ventricular enlargement with an angiotensin-converting enzyme inhibitor improved clinical outcomes with a relative risk reduction of 35%.[101] In the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial, global LVEF and WMSI were independent predictors of adverse outcome after an AMI.[102] Global LVEF did not provide additional prognostic information in multivariate analysis if WMSI was already in the model, whereas the WMSI and total number of affected segments remained significant, even after adjustment for global LVEF. In contrast, a low WMSI can prospectively identify patients at low risk after MI. A resting transthoracic echocardiogram also has been shown to be a better tool than the ECG to distinguish infarct extension from recurrent ischemia and to quantify the amount of myocardium at risk.[98,103] During AMI, the nonaffected ventricular segments are usually hyperdynamic as a compensatory mechanism. The absence of such compensatory hyperkinesis suggests multivessel coronary disease and is associated with an increased incidence of death, cardiogenic shock, progression to a worse Killip class, and reinfarction.[48,49,104,105] The prognostic role of stress echocardiography is discussed subsequently.

Echocardiography is therefore a useful tool for establishing prognosis in AMI patients. The lower the LVEF and the larger the volumes, the worse the mortality and morbidity. White and associates have reported that post-MI patients with LVEF less than 40% and end-systolic volume (ESV) more than 130 mL had 5-year survival rates of 65% and 52%, respectively.[106] The SAVE (Survival and Ventricular Enlargement) trial studied the incidence of cardiovascular death and/or LV dilation in a large population of AMI survivors, as well as the impact of LV dilation on LV chamber shape and function over a minimum 2-year follow-up.[107] In this echocardiography substudy, larger infarcts were associated with LV shape distortion and predicted progressive LV dilation, LV

dysfunction, and cardiac death.[108] However, most of these studies were performed in the prereperfusion era and medical treatment has largely improved since then. Therefore, the prognostic value of an initial echocardiographic determination of LVEF in patients who undergo rapid coronary revascularization in the early AMI setting has been reassessed.

Early revascularization limits infarct size in jeopardized myocardium, prevents recurrent ischemia, reduces LV dysfunction and subsequent LV remodeling, and decreases mortality in patients with AMI.[109] Epicardial reperfusion with primary coronary stenting is successful in more than 95% of patients with AMI, with most functional improvement occurring within 14 days.[109-111] In the VALIANT trial, Solomon and coworkers[110] showed that adequate reperfusion leads to less LV remodeling (7.4% decrease of EDV at 90 days), but progressive LV dilation occurred in one third of patients, despite successful revascularization. Similar results have been reported by Bolognese and colleagues[111] and were attributed to the no-reflow phenomenon. These results highlight the fact that the concept of successful reperfusion must include not only early and sustained epicardial patency but also optimal tissue reperfusion. Myocardial contrast echocardiography is a promising method for the assessment of myocardial blood flow and could be useful in this context.

STRESS ECHOCARDIOGRAPHY

Exercise Stress Echocardiography

For patients who are able to perform an exercise test, exercise rather than pharmacologic stress is recommended, because the exercise capacity in itself is an important predictor of outcome.[112] Either treadmill or bicycle exercise may be used; the workload and maximum heart rate achieved are usually higher with the treadmill, whereas blood pressure is higher with supine bicycle exercise. If the aim of exercise echocardiography is assessment of regional wall motion only, treadmill exercise is usually preferred. If additional Doppler information is desired, bicycle exercise allows assessment of both regional wall motion and Doppler during exercise, instead of immediately after for the treadmill.[113] Exercise stress echocardiography is a well-established technique to detect the presence and severity of CAD, which may be particularly useful for patients with an inconclusive standard stress test. Its accuracy has been shown to be superior to that of a nonimaging standard exercise ECG.[114] Stress echocardiography is not recommended in the acute phase of a suspected ACS. In patients without ongoing symptoms or with atypical chest pain, with normal serial cardiac enzyme levels and ECGs and a normal resting echocardiogram, exercise echocardiography can be performed within 24 hours. In a study of 95 patients without prior MI, the sensitivity to identify CAD of exercise echocardiography was 80% compared with 42% for exercise ECG ($P < .001$) and the specificity was 87% and 74%, respectively.[115] Armstrong and associates also reported similar results.[116] After AMI, stress echocardiography is performed to document the presence, extent, and severity of wall motion abnormalities in an effort to identify a subset of patients at high risk for recurrent ischemia, MI, and death.[117-119] Shortly after AMI was documented, exercise echocardiography increased the sensitivity from 55% to 80% and the specificity from 65% to 95% for identifying patients at risk of new ischemic events when compared with standard electrocardiographic exercise.[118] A study after uncomplicated AMI showed a fivefold increase in risk in patients with positive stress echocardiography despite the exercise ECG being positive only at a high threshold.[120]

Exercise echocardiography can be used also to assess the long-term prognosis after MI. In one study, evidence of new or worsened wall motion abnormality on stress echocardiography was associated with a relative risk of 5.1 for cardiac events or revascularization at 44 ± 11 months.[121] Krivokapich and colleagues[122] have found that an inducible wall motion abnormality on exercise echocardiography predicted cardiac events (AMI, revascularization, or death) over the next 12 months with a specificity of 86%. Most patients (80% to 95%) without major events over a long-term follow-up period did not present new regional abnormalities during the initial stress echocardiogram.[120,121,123] A normal exercise echocardiographic result is associated with an annual event rate of cardiac death and nonfatal MI of less than 1%, equivalent to that of an age- and gender-matched population.[112] These patients do not require further diagnostic evaluation unless there is a change in clinical status.[112] In patients with prior AMI, development of stress-induced regional wall motion abnormalities remote from the area of infarction has been shown to be predictive of multivessel CAD, with a sensitivity of 77% and specificity of 95%, identifying a population with a worse prognosis.[117] A meta-analysis by Fleischmann and associates[124] that compared exercise echocardiography with exercise single-photon emission computed tomography (SPECT) imaging in the diagnosis of CAD showed that echocardiography had a sensitivity similar to that of exercise SPECT imaging (85% vs. 87%) but a higher specificity (77% vs. 65%).

Pharmacologic Stress Echocardiography

In patients who cannot exercise, a pharmacologic approach can be used, with dobutamine or a vasodilator (dipyridamole or adenosine). Although vasodilators may have advantages for assessment of myocardial perfusion, dobutamine is preferred for the assessment of regional wall motion.[112]

Dobutamine Stress Echocardiography

Dobutamine has a positive inotropic effect at low doses (5 to 10 μg/kg/min), with additional inotropic and chronotropic effects at higher doses. The increase in systolic blood pressure during the infusion can be more pronounced in hypertensive patients when compared with normotensive patients. Paradoxic hypotension occasionally can be observed and is caused by the vasodilating effect of dobutamine or transient outflow tract obstruction, but is rarely caused by ischemia.[125] Beta blockers may attenuate the physiologic response to dobutamine by competing at the receptor level, and it is recommended to withhold them 24 hours before the examination when clinically possible. Among patients with normal dobutamine stress echocardiography (DSE) results, the subgroup in whom target heart rate is not achieved has a higher cardiac event rate.[126] In this same study of 3014 patients with normal DSE and 6.3 years of follow-up, age, diabetes mellitus, and failure to achieve 85% age-predicted maximal heart rate were independent predictors of mortality and cardiac events. Patients with all three of these characteristics had a 13% probability of cardiac events within the first year and a higher risk throughout follow-up.[126] Patients with a normal DSE have a slightly higher event rate than patients with normal exercise echocardiography because patients who are able to exercise tend to be younger and have fewer co-morbidities.[112]

There are two possible indications for DSE after an ACS. The first is demonstration of myocardial viability in a hypokinetic or akinetic region, which suggests that regional systolic function will improve after revascularization in the case of hibernating myocardium or spontaneously on recovery from stunning.[65,127,128] A biphasic response to increasing dobutamine doses characterized by enhanced thickening at low doses (5 to 10 μg/kg/min), indicating viability, and deterioration of thickening at higher doses (>10 μg/kg/min), indicating ischemia, is the most accurate echocardiographic

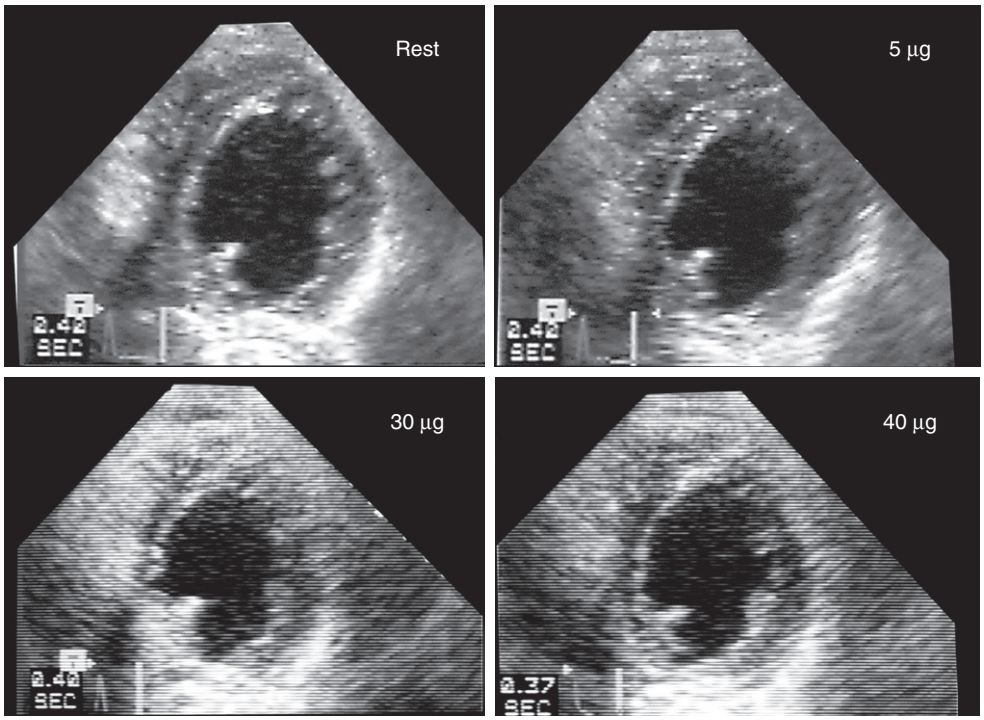

FIGURE 14–13 Dobutamine stress echocardiography shows a biphasic response with improvement of contraction in the inferior segment with a low dose of dobutamine (5 μg/kg/min) and dyskinesia of the same segment at a higher dose (30 to 40 μg/kg/min), showing myocardial viability and ischemia, respectively.

criterion to detect viable but hypoperfused myocardium (Fig. 14-13).[129] The sensitivity of DSE in predicting functional recovery, which varies depending on the protocol used, ranges from 71% to 97%, with specificity ranging from 63% to 95%.[112] The highest sensitivity for detection of viability is noted when improvement at low-dose dobutamine echocardiography is considered; highest specificity is achieved when a biphasic response occurs.[112] The more viable myocardial segments present, the higher is the probability of improvement in regional and global LVEF after revascularization. The value of low-dose DSE has been compared with that of SPECT perfusion imaging for the assessment of myocardial viability.[129-131] Several meta-analyses and studies comparing stress echocardiography with radionuclide imaging have shown that they yield similar prognostic information,[132-134] with sensitivity and specificity of 80% and 86% for echocardiography[135] and 84% and 77% for myocardial perfusion imaging, respectively.[135]

The second indication for DSE in ACS is for the assessment of the presence, severity, and extent of residual myocardial ischemia.[136-140] Greco and coworkers[141] have shown that an abnormal predischarge dobutamine stress echocardiogram obtained after uncomplicated AMI is found to be an independent predictor of outcome in multivariate analysis when other clinical and exercise variables are included; it is associated with a relative risk of 5.5 for cardiac death and MI at a mean follow-up of 17 ± 13 months. For this indication, the dobutamine infusion can be increased to 40 μg/kg/min. The overall sensitivity has ranged from 76% to 89% and the specificity from 70% to 95% for the detection of significant stenoses (50% narrowing of the arterial diameter) on coronary angiography.[105] These values are higher for the detection of multivessel or left main coronary disease. Multivessel disease detected by DSE is a better predictor of adverse clinical outcome than when it is identified by coronary angiography, a phenomenon that was shown previously with thallium-201 perfusion imaging.[142,143]

Myocardial DTI during DSE may also be used to improve its diagnostic accuracy. In a study of 92 subjects with abnormal left ventricular function at rest after AMI, an increment of peak velocity of more than 1 cm/sec with low-dose dobutamine was a predictor of functional recovery 5 months after adequate treatment.[144] In the presence of left bundle branch block (LBBB), DTI may help correctly identify patients with severe CAD, because DSE interpretation alone may be difficult with LBBB.[145] Failure to increase the peak systolic and peak early diastolic velocities by more than 2.5 cm/sec in patients with LBBB during DSE identified CAD with 88% sensitivity (for both) and 90% and 87% specificity, respectively. DTI during DSE may also be very useful for evaluation of myocardial viability.[146] Forty patients with chronic CAD and left ventricular systolic dysfunction (mean ejection fraction, 33% ± 11%) underwent ^{18}F-fluorodeoxyglucose (^{18}FDG) imaging and DSE with DTI. The sensitivity of DSE for the prediction of viability improved from 75% to 87% when DTI was performed ($P < .05$), without any change in specificity (51% and 52%). Thus, the sensitivity and specificity of DTI are superior to the visual assessment of myocardial viability. Of note, the sensitivity and specificity of DSE for the detection of viability ranges from 71% to 97% and 63% to 95%, respectively, according to the 2007 ASE recommendations document.[112]

In normal myocardium, strain and strain rate behave differently during inotropic stimulation.[147] The SR increases with increasing doses of dobutamine, whereas strain initially increases and then decreases with higher heart rates. Therefore, SR is more validated than strain during DSE. Stunned myocardium, ischemic ventricular segments, and nontransmural infarction have higher strain, SR, and postsystolic thickening than transmural necrosis.[148] The SRI determined during DSE carries additional independent prognostic information than that offered by WMSI alone.[149] Hoffmann and colleagues[150] have studied the sensitivity and specificity of SRI compared with ^{18}FDG positron emission tomography

(PET) for viability and have shown a sensitivity of 83% and a specificity of 84%, which is superior to two-dimensional DSE alone. Similar findings were also confirmed by them and by others.[148,151-154]

MCE can also be performed during stress echocardiography. Wei and associates[155] have compared the usefulness of dipyridamole stress MCE with technetium-99m sestamibi SPECT for the detection of coronary artery disease in a phase II trial. Overall concordance between the two methods was 84% (with a kappa value of 0.63). In another study of 158 consecutive patients with chest pain and possible ACS, DSE with MCE showed a sensitivity of 92%, specificity of 77%, and accuracy of 88% for detecting a coronary stenosis more than 50%.[156] Moreover, this technique was an independent predictor of outcome in patients with suspected or proven ACS, and images were inadequate in only 3% of cases. In another study of 100 patients undergoing supine bicycle or treadmill exercise echocardiography, MCE and wall motion abnormalities (WMAs) were evaluated simultaneously in real time.[157] The combination of WMA and MCE correlated well with SPECT and is a promising important addition to conventional stress echocardiography.

Vasodilator Stress Echocardiography

Dipyridamole increases local adenosine levels by inhibiting reuptake into the endothelial cells. The mechanism of action of dipyridamole as an agent to detect ischemia is believed to be a coronary steal, in which normal arteries respond by a maximal dilation, whereas arteries with significant stenosis have a reduced response, resulting in flow heterogeneity.[158] The systemic vasodilation induced by dipyridamole and the compensatory increase in heart rate also may lead to a modest increase in myocardial oxygen demand. In post-MI patients, the sensitivity of dipyridamole stress echocardiography is 68% and the specificity 100% for the detection of remote myocardial ischemia compared with coronary angiography.[159,160] In one study, dipyridamole stress echocardiography had a higher sensitivity and specificity than exercise stress echocardiography.[159] In another study of 925 patients evaluated with dipyridamole echocardiography in the post-MI setting, the presence of ischemia and its time of onset were important predictors of death and other cardiac events.[158] The use of a higher dose of dipyridamole (0.84 mg/kg) has been reported to increase the sensitivity of the test (74% to 83%) without lowering its specificity but was associated with a higher incidence of side effects (nausea, headache, flushing, dyspnea).[159,161] Finally, small studies with adenosine stress echocardiography have shown an overall sensitivity of 74% for detecting multivessel disease and only 39% for detecting one-vessel disease compared with DSE.[162] Adenosine stress is used to assess myocardial perfusion with MCE, but has not been widely used as a clinical tool.

In summary, there is a comparable level of accuracy for identifying CAD with stress echocardiography and nuclear imaging techniques. Echocardiography may be less sensitive to mild degrees of ischemia but is more specific. Although pharmacologic stress echocardiography may seem to be a more elegant approach, treadmill exercise echocardiography provides important clinical information by combining assessment of energy expenditure with the imaging technique. In patients with suboptimal transthoracic images, dobutamine TEE has been performed and seems to be a reliable tool for ischemia detection and viability assessment.[163] The availability of side by side comparison of rest and stress images with the development of digitization has markedly enhanced the ability to recognize stress-induced regional wall motion abnormalities. The introduction of tissue harmonics, which provide much better image quality and endocardial definition, especially in patients who are technically difficult to evaluate, has improved further accuracy in identifying wall motion abnormalities. Advantages of stress echocardiography compared with other techniques include shorter imaging time, lack of ionizing radiation, portability, immediate availability of the results, lower cost, and availability of other information about chamber size and function, wall thickness, valvular function, pericardial effusion, and aortic root disease.[112]

3D echocardiography is currently being investigated along with other echocardiographic modalities to enhance sensitivity and specificity for myocardial ischemia detection. 3DE imaging acquisition during exercise and pharmacologic stress echocardiography is faster than in 2DE, with at least the same specificity, sensitivity, and accuracy when compared with angiography.[164,165] Feasibility and image acquisition still remain a challenge during exercise stress echocardiography as compared with pharmacologic stress.[166] 3D strain and strain rate echocardiography are also being investigated.[167]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY AND ACUTE CORONARY SYNDROMES

TEE is a useful alternative when the transthoracic approach is technically difficult and provides suboptimal or nondiagnostic images, as may be the case in obese patients, patients with lung disease, or patients with recent cardiothoracic surgery. Assessment of regional and global ventricular function can be performed with TEE at rest or with stress, using dobutamine infusion or cardiac pacing. Detection and detailed evaluation of mechanical complications of an acute MI, such as a ruptured papillary muscle or a ventricular septal defect (see Fig. 14-10), are also possible with TEE.[168] Mitral regurgitation secondary to ischemia or infarction is a frequent finding in patients with ACS, but is occasionally difficult to determine its severity or mechanism precisely with transthoracic echocardiography.[169,170] TEE provides additional information, with important therapeutic implications, especially if mitral valve repair is being considered. TEE also can be useful for patients with ACS and atrial fibrillation (whether the cause or effect of the ischemia), particularly if the duration of the latter is unknown and the ventricular response is difficult to control. TEE is a reliable and safe method to evaluate the presence of an intracardiac thrombus before cardioversion is performed in this setting. Occasionally, a suspected embolus during the course of an ACS may represent an indication for TEE. Finally, TEE can also help rule out aortic dissection in patients with acute chest pain of uncertain origin (see Fig. 14-6).[171]

DIRECT VISUALIZATION OF CORONARY ARTERIES

Transthoracic echocardiography can visualize only a portion of the left main and proximal left anterior descending coronary arteries in approximately 60% to 70% of adult patients.[172,173] Improved visualization of the coronary arteries is possible with TEE. Yoshida and coworkers[174] have reported a sensitivity of 91% and specificity of 100% for the detection of significant proximal left main coronary narrowing (>50% diameter stenosis) with biplane TEE compared with angiography. Multiplane TEE allows enhanced visualization of extended lengths of the coronary arteries (Fig. 14-14). Tardif and colleagues have shown that the left main coronary artery with its bifurcation could be visualized in all patients with a sensitivity of 100% for detection of coronary narrowing compared with angiography.[175] The proximal and midsegments of the left anterior descending coronary artery were

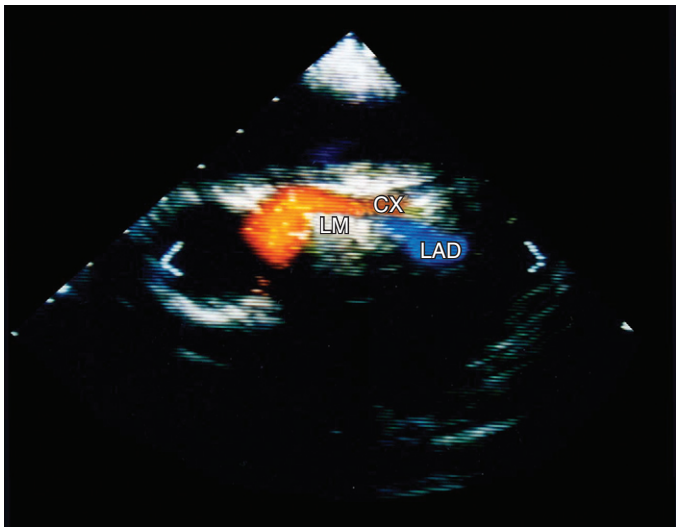

FIGURE 14–14 Transesophageal echocardiography shows flow in the left main (LM) coronary artery and its bifurcation, left anterior descending (LAD) artery, and circumflex (CX) artery.

visualized in 69% and 31%, the proximal and midsegments of the circumflex artery in 80% and 51%, and the corresponding segments of the right coronary artery in 84% and 16% of patients.

ULTRASOUND AND ACUTE CORONARY SYNDROMES

Intravascular Ultrasound

Intravascular ultrasound (IVUS) imaging uses miniaturized transducers at the tips of catheters to provide tomographic images of coronary arteries.[175,176] Coronary angiography, the traditional approach used to evaluate CAD, has well-known limitations. It provides a planar perspective of the coronary arterial lumen and not the wall, yet atherosclerosis is primarily a disease of the arterial wall. The stenosis severity may be underestimated with angiography because the reference segment with which the stenosis is compared may be involved in the diffuse atherosclerotic process (Fig. 14-15).[177] In contrast, IVUS provides cross-sectional images of the arterial lumen and wall, allowing not only determination of lumen dimensions and architecture, but also assessment of the composition, morphology, and volume of plaques, which are major determinants of the clinical expression of coronary atherosclerosis. A study of patients with angiographically mildly diseased coronary arteries revealed that half of them had narrowings of 50% of more on IVUS.[178]

IVUS examination has applications in the setting of ACS, such as for the evaluation of suspected left main CAD when doubt persists after angiography.[179] Other ambiguous lesions on angiography also can be clarified with IVUS, such as bifurcation lesions of unknown severity and problematic stenosis visualized only in a single angiographic projection. IVUS is useful for patients with recurrent chest pain after PCI to determine whether a significant narrowing is present or a technical problem occurred (e.g., persistent flow-limiting dissection, stent underdeployment, stent undersizing) in the dilated vessel.

Brachial Ultrasound

The vascular endothelium modulates vessel tone by releasing various active substances, the most important being nitric oxide (NO). Endothelial dysfunction, which results in the reduced availability of NO, disturbs the protective regulatory balance and ultimately contributes to atherogenesis, CAD progression, and possibly acute coronary events.[180] The assessment of endothelial function can be done noninvasively using high-resolution ultrasound examination of the brachial artery or angiographically by directly assessing the coronary arteries.

Anderson and coworkers[181] have shown that endothelial function measured at the brachial artery level correlates closely with that in the coronary arteries. During the brachial artery ultrasound examination, endothelial function is assessed by comparing the arterial diameter at baseline with that during hyperemia induced by the sudden increase in

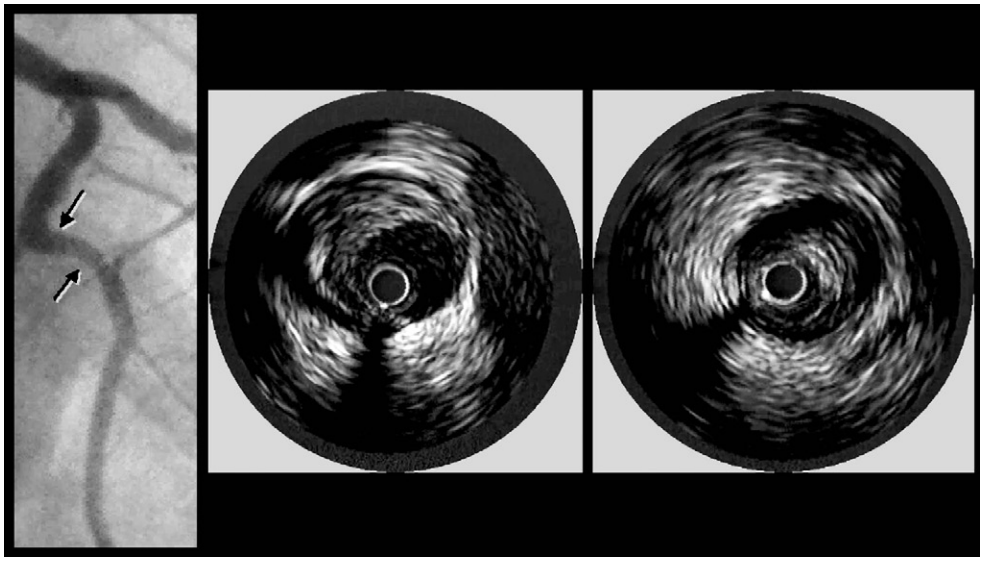

FIGURE 14–15 Angiographic (*left panel*) underestimation of the severity of coronary artery disease, revealed by intravascular ultrasound (*center and right panels*). There is mild angiographic luminal narrowing (*distal arrow*) when the lesion is compared with a pseudonormal reference segment (*proximal arrow*). On intravascular ultrasound, the reference segment shows significant plaque burden (*central panel*), and the severity of the target lesion (*right panel*) is better appreciated.

arterial flow on release of cuff-induced occlusion. Using this technique, Esper and colleagues[182] have shown that patients with ACS have endothelial dysfunction that persists after they are initially stabilized. Numerous studies have shown that risk factors for CAD impair endothelial function and that their treatment is associated with an improvement in endothelial-dependent vasodilation. In the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) study, cholesterol-lowering therapy initiated early after admission in patients with ACS rapidly improved endothelial function with only 6 weeks of treatment.[183] In patients with ACS, the impairment of endothelial function also was shown to correlate with elevated C-reactive protein levels and to resolve with normalization of markers of systemic inflammation over time.[184]

CONCLUSIONS

Rest and stress echocardiography are useful in the emergency department for the diagnostic workup of patients with chest pain. Echocardiography also provides important information about systolic and diastolic ventricular function in patients with ACS. Evaluation of residual ischemia and of myocardial viability after ACS can be done with stress echocardiography and with newer techniques, such as DTI and SRI. These techniques are also available for better quantitative evaluation of global and regional LV function during ACS. IVUS can complement the coronary angiographic evaluation in selected patients, such as those with ambiguous lesions in the left main coronary artery, at bifurcations, or at other sites. Assessment of myocardial viability and perfusion with MCE is another emerging approach with excellent correlation to radionuclide imaging, which has the potential to expand the use of cardiac ultrasound further. Echocardiography should be an integral part of the diagnostic and prognostic evaluation of patients with ACS.

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CHAPTER 15

Nuclear Cardiology Techniques in Acute Coronary Syndromes

Kenneth A. Brown

The primary goal of physicians with patients presenting with an acute coronary syndrome (ACS) is to choose a treatment strategy that optimizes outcome for each individual patient. Physicians also increasingly are asked to use medical resources in a way that minimizes the economic impact. These decisions, which involve consideration of the cost-effectiveness of an approach, necessarily involve an understanding of an individual patient's risk for important cardiac events, such as death or myocardial infarction (MI). Interventions that are expensive and that carry their own risk are most beneficial for patients who have the greatest risk of future cardiac events. Conversely, low-risk patients are unlikely to benefit from any intervention, especially one that itself has risks of complications. Knowledge of the determinants of risk in patients presenting with ACS allows physicians to make cost-effective management decisions that most benefit individual patients. In this context, nuclear cardiology techniques offer the physician important tools to help make such decisions because these techniques can assess accurately two of the most important determinants of prognosis in patients with ACS, left ventricular dysfunction and current jeopardized viable myocardium. These factors represent two interactive influences, the extent of permanent damage and the extent of future myocardium at risk. This chapter reviews current data involving the use of nuclear cardiology techniques to determine cardiac risk in ACS and shows how they can be integrated into a comprehensive, rational management strategy.

LEFT VENTRICULAR FUNCTION

Predictive Value. Determination of left ventricular function using radionuclide angiography has been shown to be a powerful predictor of outcome in patients who present with an acute MI.[1-5] The left ventricular ejection fraction measured by radionuclide techniques probably has been the most valuable index of function because of its reproducibility and its consistent predictive value. In the MPRG (Multicenter Post Infarction Research Group) study, patients who had presented with an acute MI underwent predischarge radionuclide angiography.[1] The 1-year cardiac mortality rate was exponentially inversely related to left ventricular ejection fraction (Fig. 15-1). Cardiac mortality increased, especially after the ejection fraction decreased to less than 40%.

The influence of left ventricular function on outcome has persisted, even as the overall outcome after acute MI has improved with the introduction of thrombolysis and percutaneous coronary interventions. In the TIMI trial, overall cardiac death rate was lower than in the MPRG trial, but the increased relationship between ejection fraction and annual cardiac mortality rate was retained (see Fig. 15-1).[2] Similarly, the CAMI study evaluated the outcome of patients with acute MI in the thrombolytic era of the 1990s.[3] These investigators found an inverse relationship between ejection fraction and 1-year cardiac mortality that matched the MPRG findings closely (Fig. 15-2). The differences were greatest at the low end (ejection fraction < 20%), possibly reflecting the ameliorative effects of angiotensin-converting enzyme inhibitor and beta blocker treatment that became the standard of care in the 1990s.

Several other studies have confirmed the important prognostic value of ejection fraction in patients receiving thrombolysis. Simoons and colleagues[4] found that 5-year survival was only approximately 40% in patients with left ventricular ejection fraction less than 30% compared with greater than 90% survival when the ejection fraction was higher than 40%. Similarly, Dakik and coworkers[5] found the risk of cardiac events increased as ejection fraction decreased in patients receiving thrombolysis for acute MI. Event-free survival was approximately 75% for patients with an ejection fraction of 40% compared with survival less than 25% for patients with an ejection fraction less than 40%.

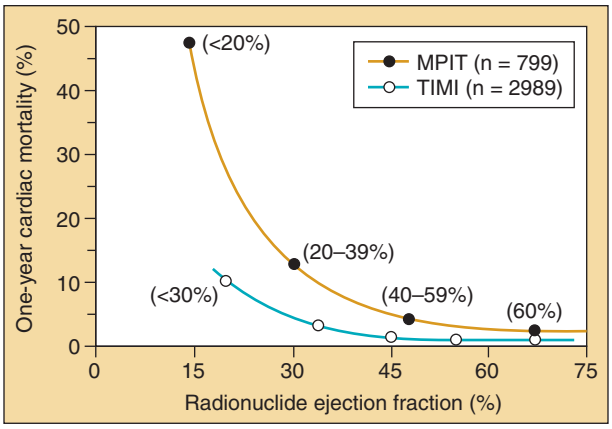

FIGURE 15–1 One-year cardiac mortality rate as a function of radionuclide angiographic ejection fraction in the Multicenter Post-Infarction Research Group Trial (MPIT) and the Thrombolysis in Myocardial Infarction (TIMI) trial. Mortality rate increases as ejection fraction decreases. The overall mortality rate was higher in the MPIT cohort. *(From Bonow RO: Prognostic assessment in coronary artery disease: Role of radionuclide angiography. J Nucl Cardiol 1994;1:280-291.)*

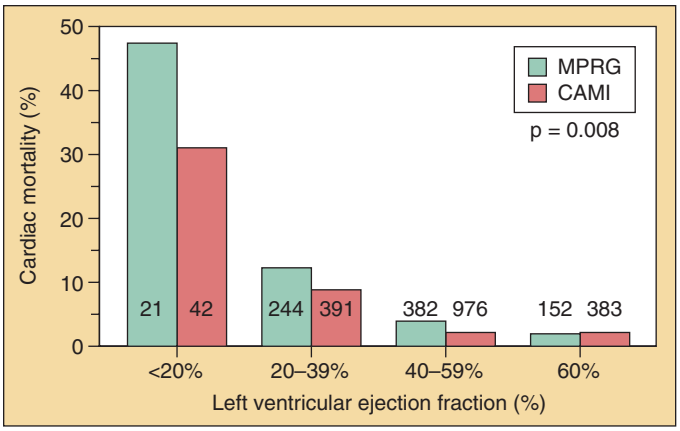

FIGURE 15–2 One-year cardiac mortality as a function of radionuclide left ventricular ejection fraction in the Multicenter Postinfarction Research Group (MPRG) trial performed before the reperfusion era then in the Canadian Assessment of Myocardial Infarction (CAMI) study. Cardiac mortality in patients with poor function (ejection fraction < 20%) was better in the more recent CAMI cohort. *(From Rouleau JL, Talajik M, Sussex B, et al: Myocardial infarction patients in the 1990s—their risk factors, stratification and survival in Canada: The Canadian Assessment of Myocardial Infarction [CAMI] Study. J Am Coll Cardiol 1996;27:1119-1127.)*

Limitations of Measurement of Left Ventricular Function and Dynamic Changes

Although left ventricular ejection fraction has a powerful ability to predict cardiac mortality after acute MI, it has some limitations. First, although the measurement of ejection fraction itself with radionuclide angiography is highly reproducible and accurate,[6] indices of left ventricular function measured early after MI may change over time, even in the short term. This change may reflect evolving post-MI cardiac physiology, including segmental transient stunning and hyperkinesis. Christian and associates[7] have found that 16% of patients with acute MI showed a rise in ejection fraction of 8% determined by radionuclide angiography between discharge and 6 weeks. At discharge, the ejection fraction in this group was less than that predicted based on the size of the MI, as determined by myocardial perfusion imaging. This suggests that the rise in ejection fraction at 6 weeks reflects a resolution of myocardial stunning. Conversely, 19% of patients showed a decrease in ejection fraction of 8% by 6 weeks. Although remodeling can explain a decrease in left ventricular function over time after acute MI, these patients had a discharge ejection fraction that was greater than that predicted based on the infarct size, suggesting that the decrease in ejection fraction over 6 weeks more likely reflected resolution of early hyperkinesis in the noninfarct zone.

Hibernating myocardium is another factor that may affect left ventricular function in the setting of prior MI. To the extent that it is present, hibernating myocardium is important to identify because coronary revascularization can improve left ventricular function and survival.[8] Although hibernating myocardium may be an important factor in determining prognosis and management in chronic ischemic cardiomyopathy, its role in acute MI is likely to be small. Aside from the transient influences of stunning or hyperkinesis, left ventricular ejection fraction probably primarily reflects the permanent damage done by acute MI, which accounts for its strong prognostic value. It is clear that ejection fraction, reflecting the extent of scar, is a powerful predictor of mortality, but it reflects what has already occurred. Although beta blockers and angiotensin-converting enzyme (ACE) inhibitors may increase survival, it is an unproved hypothesis that revascularization alters outcome in this setting in the absence of stunning, hibernation, or other critical artery stenoses.

An outcome that can be altered by surgical or percutaneous intervention is more likely related to the extent of jeopardized viable myocardium that is present after the insult of the acute MI. As is reviewed subsequently, there are much data to suggest that the presence and extent of jeopardized viable myocardium defined by stress nuclear myocardial perfusion imaging (MPI) is the most important predictor of outcome in patients with acute MI. There is an important interaction between the extent of permanent damage (scar) and that of additional viable myocardium at risk.

PROGNOSTIC VALUE OF JEOPARDIZED VIABLE MYOCARDIUM DETERMINED BY STRESS NUCLEAR MYOCARDIAL PERFUSION IMAGING

Predictive Value. Because reversible defects on stress MPI accurately identify and quantify jeopardized viable myocardium, this technique can play an important role in assessment of risk after acute MI (Box 15-1). Probably the most consistent observation reported in the literature regarding the

BOX 15-1 Advantages of Nuclear Myocardial Perfusion Imaging for Evaluating Patients After Myocardial Infarction

- Increased sensitivity for detecting ischemia and multivessel disease
- Increased prognostic value—jeopardized viable myocardium predicts death or myocardial infarction
- Ability to localize ischemia to individual coronary territories
- Distinguishing infarct zone from noninfarct zone myocardium at risk
- Evaluation of left ventricular function and perfusion simultaneously
- Can use vasodilator stress as adjuvant, allowing earlier risk stratification

prognostic value of stress nuclear MPI is that the presence and extent of transient defects, reflecting jeopardized viable myocardium, predict important cardiac events.[9,10] A direct relationship between myocardium at risk identified by nuclear MPI and patients at risk for cardiac events first was reported by Brown and colleagues in 1983.[11] They compared the prognostic value of exercise thallium-201 imaging, exercise treadmill testing, coronary angiography, and clinical data and found that the best predictor of cardiac death or nonfatal MI was the number of segments with transient thallium-201 defects. These early findings were confirmed and expanded by many investigators. Ladenheim and associates[12] found that among clinical and scintigraphic indices, the number of reversible perfusion defects on stress thallium-201 images was the best predictor of future cardiac events. Similar observations were made in a wide clinical spectrum of patients—patients with suspected coronary artery disease (CAD) or known angiographic CAD, patients undergoing noncardiac surgery, patients with remote prior MI, and, as discussed later, patients presenting with unstable angina or acute MI. The powerful predictive value of nuclear MPI is retained whether the stress agent is exercise, vasodilator stress, or an adrenergic agent and regardless of whether the perfusion tracer is thallium-201 (^{201}Tl), technetium-99m (^{99m}Tc)-based agents such as sestamibi or tetrofosmin, or positron emission tomography (PET) imaging agents.[13-15] For each of these modalities of imaging and patient cohorts, the most consistent finding has been that cardiac risk is related directly to the presence and, more importantly, the extent of jeopardized viable myocardium.

Acute ST-Segment Elevation Myocardial Infarction

Exercise Nuclear Imaging

The prognostic value of exercise MPI in the post-MI setting first was reported by Gibson and coworkers.[16] Predischarge submaximal exercise ^{201}Tl-MPI was compared with clinical, exercise, and coronary angiographic data for predicting subsequent cardiac events. Reversible ^{201}Tl defects, defects involving multiple coronary territories, and increased lung ^{201}Tl uptake (reflecting left ventricular dysfunction) were the most important prognostic MPI variables. Compared with clinical or coronary angiography, these indices were significantly more sensitive for detecting patients at risk for cardiac events (Fig. 15-3). The greater sensitivity for detecting the patient at risk translated into a greater ability to identify the low-risk patient who is unlikely to benefit from further invasive or interventional procedures. Subsequently, many studies confirmed the prognostic value of exercise MPI in patients presenting with an acute MI.[9,10] Wilson and colleagues[17] showed that in patients with acute MI and single-vessel CAD, late cardiac events were related to the presence and extent of transient defects on submaximal exercise MPI but not to clinical or exercise electrocardiographic data. Travin and associates[18] have used regression analysis of clinical, exercise electrocardiography, and exercise sestamibi single-photon emission computed tomography (SPECT) MPI variables in patients with acute MI and found that only the number of reversible defects is a significant predictor of cardiac events (Fig. 15-4). As in patients with chronic stable CAD, there is compelling evidence that the risk of future cardiac events in patients with acute MI is strongly related to the presence and, more importantly, the extent of jeopardized viable myocardium. Interesting data using a novel, ischemia-sensitive perfusion agent has confirmed the incremental prognostic value of residual jeopardized viable myocardium post-MI. Iodine-123 beta-methyl iodophenyl pentadecanoic acid (^{123}I-BMIPP) uptake is related to myocardial perfusion

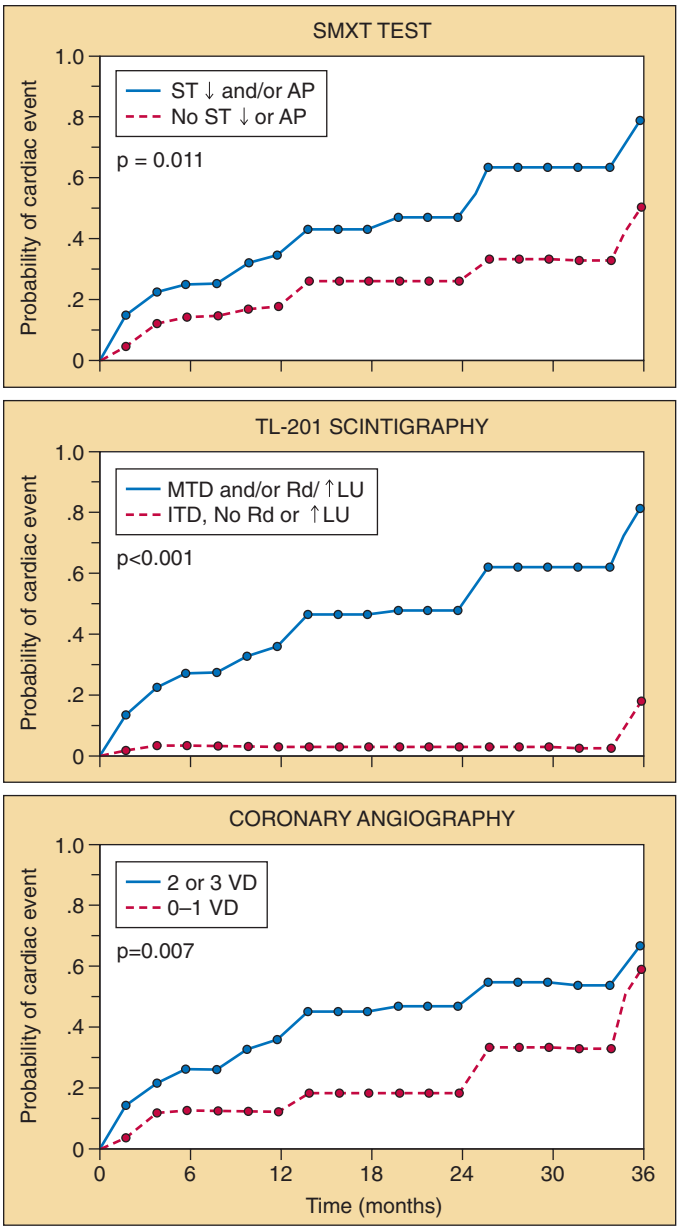

FIGURE 15–3 Cumulative probability of cardiac event over time as a function of high-risk *(solid line)* and low-risk *(dashed line)* criteria for submaximal exercise test (SMXT) *(top panel)*, thallium-201 (TL-201) imaging *(middle panel)*, and coronary angiography *(lower panel)*. Thallium-201 imaging better separated high-risk from low-risk patients. AP, angina pectoris; LU, lung uptake; MTD, multiple vascular territory thallium-201 defects; Rd, redistribution (reversible defects); ST↓, ST-segment depression; VD, vessels diseased. *(From Gibson RS, Watson DD, Craddock GB, et al: Prediction of cardiac events after uncomplicated myocardial infarction: A prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983;68:321-336.)*

but is also sensitive to metabolic changes induced by ischemia.[19] When imaged in conjunction with resting ^{201}Tl imaging, a mismatch in uptake (normal ^{201}Tl uptake, reduced ^{123}I-BMIPP uptake) indicates an area of myocardium with normal resting flow but with a recent history of ischemic insult. Nanasato and coworkers[20] have found that in patients with acute ST-segment elevation MI (STEMI) treated with primary coronary intervention ^{123}I-BMIPP–^{201}Tl mismatch and total ^{123}I-BMIPP defect score added significant prognostic value to left ventricular function and extent of angiographic CAD for predicting cardiac events. For all-cause mortality, mismatch plus extent of ^{123}I-BMIPP defects doubled the global

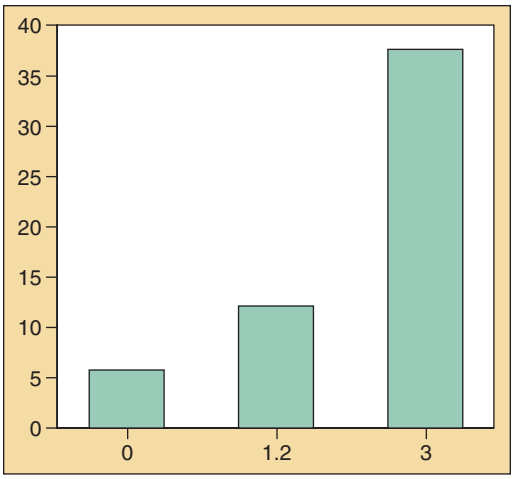

FIGURE 15–4 Cardiac event rate as a function of the number of reversible defects on exercise ^{99m}Tc-sestamibi imaging after uncomplicated myocardial infarction. The cardiac event rate rises as the number of reversible defects increases. *(Adapted from Travin MI, Dessouki A, Cameron T, Heller GV: Use of exercise technetium-99m sestamibi SPECT imaging to detect residual ischemia and for risk stratification after acute myocardial infarction. Am J Cardiol 1995;74:665-669.)*

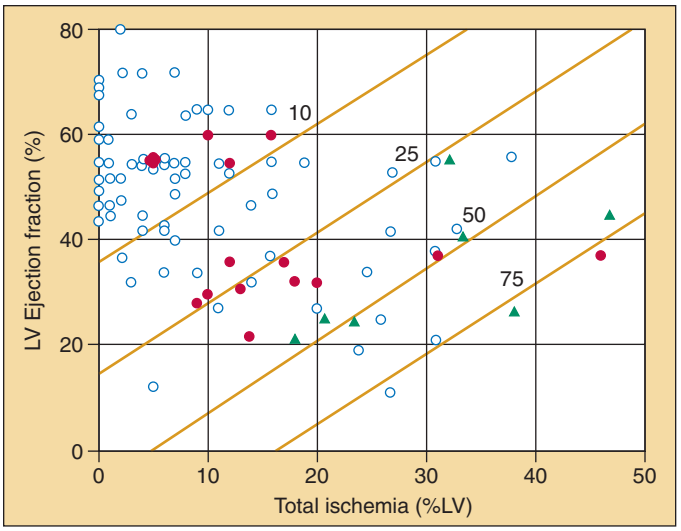

FIGURE 15–5 One-year cardiac risk of death or nonfatal myocardial infarction as a function of LV ejection fraction and total ischemia on adenosine thallium-201 imaging after myocardial infarction. *Diagonal lines* represent isobars of percent risk. For a given ejection fraction, risk increases as total ischemia increases. For a given degree of ischemia, risk increases as ejection fraction decreases. *(From Mahmarian JJ, Pratt CM, Nishimura S, et al: Quantitative adenosine 201Tl single-photon emission computed tomography for the early assessment of patients surviving acute myocardial infarction. Circulation 1993;87:1197-1210.)*

chi-square test results of the predictive model compared with cardiac catheterization data.

Indirect Markers of Ischemia

Several indirect markers of ischemia on stress MPI have been shown to have adverse prognostic implications, although they have been incompletely studied in patients with acute MI. Increased ^{201}Tl lung uptake on exercise MPI has been shown to reflect stress-induced rises in left ventricular filling pressure[21,22] and has been associated with severe CAD and resting and exercise-induced left ventricular dysfunction.[23-26] It has been shown to predict an increased risk of cardiac events in patients with acute MI and with chronic coronary disease.[16,27,28] Transient left ventricular dilation on stress compared with rest imaging also has been related to extensive CAD and left ventricular dysfunction, and has been associated with increased risk of cardiac events.[29-32] More data are needed to understand the full clinical implications of these findings, especially in patients with ACS.

Vasodilator Perfusion Imaging

Vasodilator stress may have a particular advantage over exercise as an adjunct to MPI in patients with acute MI. It produces a greater hyperemic stimulus compared with submaximal exercise and consequently has been shown to have greater sensitivity for detecting CAD when used with stress MPI,[33] an important issue for risk stratification in the post-MI setting. Leppo and coworkers[34] were the first to show that vasodilator stress, using intravenous dipyridamole, with ^{201}Tl-MPI predicted cardiac events when performed 10 to 16 days after MI. Compared with clinical and radionuclide ventriculographic left ventricular function data, these investigators found that reversible ^{201}Tl defects were the only significant predictors of late cardiac death or MI and identified 92% of patients at risk for such future cardiac events. Subsequently, other investigators confirmed the predictive value of reversible defects on dipyridamole-MPI, reflecting jeopardized viable myocardium in patients with acute MI.[9,10]

Adenosine Stress Perfusion Imaging. Adenosine also has been found to be valuable as a vasodilator adjuvant for stress MPI after MI. Mahmarian and colleagues[35,36] have described the early and late prognostic value of adenosine ^{201}Tl-SPECT MPI in patients with acute MI. Imaging detected jeopardized viable myocardium in 59% of infarct zones and in 92% of noninfarct zones supplied by a stenotic artery. Angiographic patency did not predict the presence or extent of jeopardized myocardium. In-hospital cardiac events occurred in 43% of patients with significant reversible defects compared with 9% without significant reversibility. Over a mean 16-month follow-up, the best predictors of cardiac events were extent of reversible ^{201}Tl defects and ejection fraction. The authors showed that adenosine MPI data had significant incremental prognostic value when added to clinical and angiographic data, improving the ability to predict cardiac events twofold to fivefold. The negative impact of MPI ischemia on outcome was additive to that of the left ventricular ejection fraction (Fig. 15-5), consistent with the paradigm that the extent of residual jeopardized viable myocardium and left ventricular function are the primary determinants of outcome after MI.

Dobutamine Stress Perfusion Imaging. Dobutamine adrenergic stimulation offers an alternative to vasodilator stress as an adjunct to MPI in patients unable to exercise. This alternative is particularly useful for patients with contraindications to vasodilators, such as bronchospasm, recent caffeine or methylxanthine exposure, high-degree atrioventricular block, or hypotension. Previous reports have described sensitivity and specificity for detecting CAD comparable to exercise or vasodilator stress nuclear imaging.[37] Several studies have shown that dobutamine stress MPI has significant prognostic value in patients with stable CAD[38-42] or before noncardiac vascular surgery.[43-45] Data in stable coronary disease suggest that, as with exercise MPI, the risk of death or MI is related directly to the extent of jeopardized viable myocardium on dobutamine stress MPI.[39] Few data are available, however, for dobutamine MPI in the post-MI setting. In contrast to vasodilators, dobutamine produces a much more marked increase in heart rate and blood pressure, leading to induction of true ischemia in the setting of coronary lesions, rather than just heterogeneity of hyperemia. Consequently, although dobutamine stress MPI can be performed safely, it needs to be applied more cautiously in the post-MI setting, especially the early post-MI setting.

Coma-Canella and colleagues[45] have performed dobutamine stress ^{201}Tl-SPECT and radionuclide angiography a mean of 16 days after MI. They found that extent of ischemia on SPECT imaging correlated with abnormal dobutamine-induced regional wall motion. No angiographic or prognostic data were reported. Elhendy and associates[46] have reported a sensitivity of 74% and 71% for detecting remote and infarct-related coronary disease, respectively, using dobutamine stress ^{201}Tl-SPECT in 71 patients more than 3 months after acute MI. Specificity was 80% to 83%. These authors also reported similar sensitivities, specificities, and predictive values for dobutamine stress MPI and echocardiography in detecting remote and infarct-related coronary disease in patients with prior MI.[47] In this cohort, most of the patients were studied several years after MI. In contrast, Lancellotti and coworkers[48] have compared dobutamine stress MPI and echocardiography performed a mean of 5 days after MI. In this small select cohort of 75 patients, there were no serious dobutamine-related complications. MPI was a sensitive and specific predictor of infarct-related stenoses (70% and 83%) and multivessel disease (67% and 93%) and was comparable to stress echocardiography.

Dobutamine stress MPI seems to assess accurately post-MI coronary anatomy, and there is internal consistency between dobutamine-induced perfusion defects and inducible wall motion abnormalities. Determination of the prognostic implications and the safety of dobutamine stress MPI awaits further data, however.

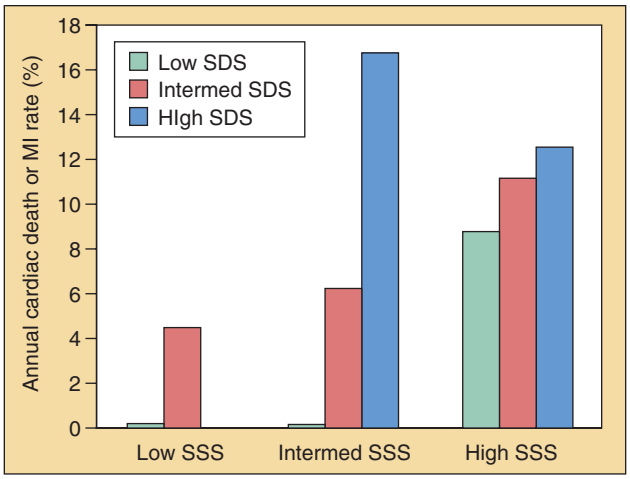

FIGURE 15–6 Annual cardiac death or MI rate as a function of the size of the perfusion defect and degree of reversibility in patients undergoing vasodilator nuclear myocardial perfusion imaging early after acute MI. For a given summed stress score (SSS) reflecting the stress perfusion defect, cardiac risk increased as the summed difference score (SDS), reflecting reversibility and thus jeopardized viable myocardium, increased. *(From Brown KA, Heller GV, Landin RJ, et al: Early dipyridamole Tc99m-sestamibi SPECT imaging 2-4 days after acute myocardial infarction predicts in-hospital and post-discharge cardiac events: Comparison with submaximal exercise imaging. Circulation 1999;100:2060-2066.)*

Early Post–Myocardial Infarction Risk Stratification

In addition to its greater sensitivity for detecting CAD, vasodilator stress MPI has other advantages that can allow it to play an important role in the early in-hospital management of post-MI patients. In contrast to exercise, vasodilator stress induces only modest changes in determinants of myocardial oxygen demand.[49-51] In addition, the hemodynamic effects are brief (adenosine) or rapidly reversible (dipyridamole).[26,27] As a consequence, risk stratification with vasodilator stress MPI can be performed safely, potentially much earlier than exercise after acute MI. Management decisions can be made sooner than the standard 5- to 7-day post-MI, predischarge evaluation, potentially shortening hospitalization and reducing costs. In addition, identifying high-risk patients and directing appropriate treatment sooner can prevent early cardiac events.[52] Brown and colleagues[52] first reported a series of 50 patients who underwent dipyridamole ^{201}Tl-MPI 1 to 4 days (mean, 2.6 days) after acute MI. No serious adverse effects occurred with dipyridamole administration. Clinical, electrocardiographic (ECG), cardiac catheterization, and ^{201}Tl-MPI data were analyzed, and the only significant predictor of in-hospital ischemic cardiac events was the presence of reversible defects in the infarct zone. Nine of 20 patients (45%) with infarct zone reversible defects had in-hospital ischemic cardiac events compared with 0 of 30 patients without ($P = .0001$). Over a mean 12-month follow-up period, there were three additional cardiac events in patients with reversible defects, whereas patients without reversible defects remained free of cardiac events. It seems that early risk stratification with dipyridamole MPI could identify high-risk patients, who could be referred early to invasive procedures and revascularization, and low-risk patients, who could be discharged early safely without further interventions.

These pilot data led to a much larger multicenter study involving 451 patients that was designed to compare the prognostic value of dipyridamole ^{99m}Tc-sestamibi SPECT MPI performed 2 to 4 days after acute MI with standard submaximal exercise MPI obtained at 6 to 12 days.[54] Confirming the pilot safety data, no significant adverse effects were attributable to the dipyridamole infusion. Clinical and stress test data were compared with MPI data, including the following: a summed stress score, reflecting the size and severity of the defect on the stress images; and a summed difference score, reflecting the degree of reversibility between stress and rest images. The dipyridamole MPI summed stress and reversibility scores were significant multivariate predictors of in-hospital cardiac events. Patients were followed for a mean of 2 years. The dipyridamole MPI summed stress, rest, and difference scores were each significant multivariate predictors of future cardiac death or MI. Consistent with the theme emphasized in this review, indices of scar (summed rest score) and ischemia (summed difference score) were significant determinants of outcome after MI. Dipyridamole MPI was better able to risk-stratify patients than submaximal exercise MPI. This was manifested as a greater ability to separate low-risk from high-risk patients. Not only were significant prognostic data available earlier with dipyridamole MPI compared with submaximal exercise MPI, but the information was superior at separating high-risk from low-risk patients.

There was an important interaction between the size of the initial stress defect and the degree of reversibility for determining individual patient risk. For a given size of stress defect, cardiac risk increased as the degree of reversibility, reflecting jeopardized viable myocardium, increased (Fig. 15-6). Patients with a small defect (low summed stress score) had an overall annual cardiac death or MI rate of 2%, but this decreased to 0% in patients with little or no ischemia and increased to 4% in patients whose defect was primarily reversible. The interaction was greatest in patients with intermediate-sized stress defects. The overall annual event rate was 5%, but knowing this degree of jeopardized viable myocardium allowed further risk stratification—0% with no or small ischemia increasing to 6% with intermediate ischemia and 17% with extensive ischemia. The interaction was least in patients with large stress defects because the event rate remained high in patients with extensive infarction but little or no ischemia.

The predictive value of early post-MI vasodilator stress MPI has been confirmed by the larger INSPIRE trial,

comprised of 728 patients undergoing gated adenosine MPI a median of 3 days post-MI.[55] MPI results stratified patients into low-, intermediate-, and high-risk patients, with 1-year death-MI rates of only 1.8% in patients with small perfusion defects and increasing progressively as the perfusion defect exceeded 20% of the left ventricular (LV) myocardial volume (9.2%; 1-year death-MI) and also had moderate or greater (>10%) ischemia (11.6%; 1-year death-MI). This study also incorporated the evaluation of LV function into the analysis and found that the cardiac event rate increased as LV ejection fraction (LVEF) decreased. Multivariate analysis has shown that total stress perfusion defect size, which incorporates scar plus ischemia, is the best and only significant predictor of death or MI.

These studies show that vasodilator stress MPI can be performed safely early in the post-MI period and provides powerful prognostic data not only sooner than, but also superior to, submaximal exercise MPI data. It allows identification of high-risk patients, who are candidates for early intervention, and low-risk patients, who can be considered for early discharge.

Selective Versus Nonselective Invasive Approach After an Acute Myocardial Infarction (ST-Segment Elevation)

Implicit in an ischemia-guided selective approach to cardiac catheterization and revascularization for the patient with acute MI is the assumption that patient outcome will be at least as good as a nonselective approach, in which every patient is referred for catheterization, and revascularization decisions are based on coronary anatomy. There are now substantial data to support such an assumption (Box 15-2).[56-59] The TIMI IIB trial compared the outcome of 3262 patients presenting with acute STEMI who were randomized to angiography and anatomy-guided revascularization versus a conservative, or ischemia-guided approach, in which patients were referred to angiography and revascularization only if there was symptomatic or exercise-induced electrocardiographic evidence of ischemia.[56] The composite end point of death or MI at 6 weeks occurred in 10.9% of the invasive group compared with 9.7% of the ischemia-guided group (P = not significant). Although the more sensitive nuclear MPI was not used in the conservative ischemia-guided group, the outcome was at least as good as in the nonselective invasive group. Similar findings were reported from the SWIFT trial,[57] which compared the outcome of patients with acute ST-segment elevation treated with thrombolysis and randomized to early invasive, anatomy-guided intervention versus conservative, ischemia-guided intervention. The death or MI rate at 1 year was 19.1% versus 16.6% in the invasive and conservative groups, respectively (P = not significant). The TOPS study included patients who presented with acute STEMI, received thrombolysis, had angiographically significant infarct vessel disease (>50% stenosis), but had a negative stress functional study (generally, ^{201}Tl-MPI).[58] Patients were randomized to medical treatment without intervention or to delayed coronary angioplasty at days 4 to 14. The infarct-free survival at 12 months was 100% in the medical treatment group versus 89% in the angioplasty group (P = .07). The infarcts that occurred in the angioplasty group all were procedure-related. Functional noninvasive risk stratification was able to identify a population of patients at low risk for cardiac events treated medically who are not benefited (and possibly harmed) by intervention.

A registry study emphasized how a nonselective approach to coronary intervention in patients with acute MI may lead to a poorer outcome even when performed by experts. Dakik and Verani[59] reported the disposition and outcome of a large consecutive series of patients admitted to Baylor Methodist Hospital, a major cardiac tertiary care hospital, with acute MI or unstable angina. The first diagnostic test was cardiac catheterization in 72% of 1704 patients admitted with acute MI; only 6% had a nuclear MPI, and only 1% had a stress test as the first diagnostic study. The overall revascularization rate was 49%, but was much higher in patients evaluated solely by angiography (70%) than in patients undergoing stress MPI (29%; $P < .001$). The higher revascularization rate did not translate into a better outcome, however. The in-hospital mortality rate was significantly higher in patients evaluated with angiography alone (10%) compared with patients evaluated with nuclear MPI (1%). The differences were more striking among patients undergoing coronary revascularization (Fig. 15-7). The mortality was 10% in patients evaluated with angiography alone compared with 0% in patients evaluated with nuclear MPI. These differences could not be explained by a higher clinical risk pattern in the angiography group. There were no differences in the frequency of hypertension, diabetes mellitus, or anterior MI, and patients undergoing angiography were younger (P = .05) and tended to have less heart failure. Even in a major cardiac medical center, a nonselective invasive approach does not lead to a better outcome but may be associated with a worse outcome. Performing invasive and interventional procedures only can add risk to patients who already have a low risk of

BOX 15-2 Summary of Randomized Trials Evaluating Selective Versus Nonselective Strategy of Catheterization after Myocardial Infarction

ST-Segment Elevation MI Following Thrombolysis

Outcome not different with selective (ischemia-guided) catheterization or revascularization compared with nonselective (anatomy-guided) strategies

- TIMI IIB trial
- SWIFT trial
  - If no provocable ischemia, event-free survival not improved with intervention; 100% event-free survival with medical treatment
- TOPS trial

Unstable Angina and Non–ST-Segment Elevation MI

Outcome not different with selective (ischemia-guided) catheterization or revascularization compared with nonselective (anatomy-guided) strategies

- TIMI IIIB
  - Outcome better with selective (ischemia-guided) strategy
- VANQWISH trial
  - Use of catheterization and revascularization more efficient with ischemia-guided strategy
- TIMI IIIB trial
- VANQWISH trial
  - Recent cost-effectiveness data favoring ischemia-guided strategy
- FRISC II trial
  - Outcome better with invasive strategy
  - Nuclear imaging not used
  - High threshold for crossover to catheterization or revascularization (3-mm ST-segment depression)
- TACTICS-TIMI 18 trial
  - Glycoprotein IIb/IIIa platelet inhibitors used in all patients
  - Stents used in interventional group
  - Overall outcome better with nonselective interventional strategy
  - Benefit of nonselective interventional strategy limited to high-risk subgroup (40% of total cohort)
  - Outcome in low-risk subgroups (60% of total cohort) not different between strategies

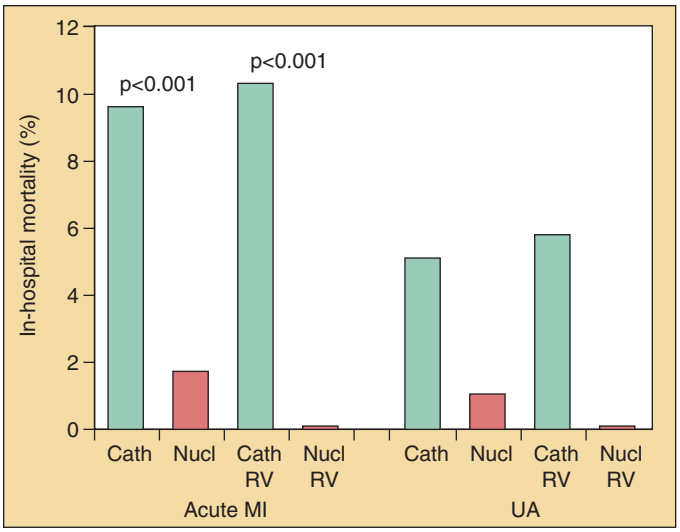

FIGURE 15–7 In-hospital mortality rate in acute myocardial infarction (MI) or unstable angina (UA) patients undergoing cardiac catheterization (Cath) alone as a diagnostic procedure versus patients undergoing nuclear imaging (Nucl). Analogous mortality data are shown for patients undergoing coronary revascularization (RV). In-hospital mortality rate was significantly lower in patients receiving nuclear imaging as part of their evaluation compared with cardiac catheterization alone. *(Adapted from Dakik HA, Verani MS: Use of invasive and nuclear stress testing in patients with acute ischemic syndromes in a large, urban, university-affiliated hospital. J Nucl Cardiol 2000;7:328-332.)*

cardiac events. The better outcome of patients undergoing nuclear MPI as part of their post-MI evaluation presumably was related to the ability of this procedure to distinguish such low-risk patients from the high-risk cohort that would benefit from revascularization.

Compelling data exist suggesting that a selective, ischemia-guided strategy of invasive procedures and interventions leads to an equivalent, if not better, outcome compared with a nonselective approach in patients with STEMI who receive thrombolysis. Conversely, there is no convincing evidence that post-MI patients do better with coronary intervention in the absence of provokable ischemia. Whether newer advances in intervention, such as stents, will alter this conclusion is currently unknown and requires further study. Advances in the medical treatment of acute MI patients also have occurred, including the introduction of glycoprotein IIb/IIIa inhibitors, statins, and ACE inhibitors and greater recognition of the benefit of beta blockers.

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Patients with unstable angina or non-ST-segment elevation MI (NSTEMI) are another ACS cohort for whom traditional management has involved an aggressive invasive approach because of the presumption that the syndrome is an immediate precursor to MI (unstable angina) or is associated with an incomplete and unstable infarction (NSTEMI).

Unstable Angina. The unstable angina cohort is heterogeneous, and it is necessary to distinguish truly refractory unstable patients from "stabilizable" patients responsive to medical treatment. Many studies have shown that antiplatelets, anticoagulants, beta blockers, and calcium antagonists can reduce the death and MI rate in patients presenting with unstable angina.[60] There also are data that intensification of an existing medical regimen can reduce the medically refractory rate.[61] Patients who present with unstable angina who continue to have recurrent chest pain require coronary revascularization. In patients who are stabilized with institution or intensification of medical treatment, however, it is reasonable to ask whether noninvasive evaluation with stress MPI can distinguish low-risk patients, whose outcome is unlikely to be improved with revascularization, from high-risk patients, who are likely to benefit.

Risk stratification in patients with unstable angina first was evaluated by Hillert and colleagues,[62] who performed submaximal exercise ^{201}Tl-MPI in patients who were stabilized after admission with unstable angina. Over a 12-week follow-up period, 15 of 19 patients with reversible defects developed MI or had class III or IV angina compared with only 2 of 18 patients without reversible defects ($P < .001$). In a larger series of 158 patients admitted with an acute non-MI coronary syndrome, an acute MI or cardiac death occurred in 21% of patients with reversible exercise ^{201}Tl defects compared with only 3% without reversible defects over a median 14-month follow-up period.[63] When compared with Holter electrocardiography, stress electrocardiography, and cardiac catheterization data, the extent of reversible defects on MPI was the only significant multivariate predictor of cardiac events.[64]

Brown[65] has described a series of 52 patients presenting with unstable angina who responded to initial medical treatment and underwent exercise ^{201}Tl-MPI before discharge. The only significant multivariate predictor of cardiac death or MI over a 39-month follow-up period was the presence of reversible defects. Cardiac death or MI occurred in 26% of patients with reversible defects compared with only 3% of patients without reversible defects (<1% annual rate). Stress electrocardiography had no predictive value. These findings were confirmed in a similar cohort of 126 patients.[66] Over a mean 12-month follow-up period, 10 of 40 patients (25%) with reversible defects had cardiac death or MI compared with only 1 of 86 patients (1%) without reversible defects ($P < .001$). Similar to the findings of Brown,[65] neither fixed perfusion defects nor exercise electrocardiography predicted cardiac events.

Although most of these studies involved small cohorts, they are remarkably consistent and are consistent with data in other coronary heart disease patient cohorts. Reversible defects, reflecting jeopardized viable myocardium, predict important cardiac events. Table 15-1 summarizes the data for studies using death and MI as end points. Reversible defects identify a high-risk cohort with a 20% to 26% risk of cardiac death or MI over a 1- to 3-year time frame. Such a cohort would be expected to benefit from coronary revascularization. Patients without reversible defects, especially patients with normal perfusion, have a low risk of cardiac events, however, and are not likely to benefit from intervention.

Non–ST-Segment Elevation Myocardial Infarction. Similar to unstable angina, patients who present with NSTEMI (formerly non–Q-wave) MI are a heterogeneous population. Not all such infarctions are subendocardial or incomplete. Pathologic studies have shown that although the infarcts tend to be smaller, the transmural distribution is not much different from Q-wave or ST-segment elevation MI.[67] The smaller size of the non–Q-wave infarction is associated with a higher frequency of residual jeopardized viable myocardium. Gibson and coworkers[68] have evaluated clinical and stress MPI results in patients with acute non–Q-wave MI and found that infarct zone reversible defects were present in 60% of patients compared with 36% with Q-wave MI ($P < .01$). Only 1 of 35 (3%) non–Q-wave MI patients without infarct zone reversibility on MPI developed recurrent MI over a mean 27-month follow-up period compared with 15 of 52 patients (29%) with infarct zone reversibility.[68] Stress MPI also has predictive value in patients with NSTEMI and atypical presentation. In a series of 156 patients with elevated troponin levels but without typical symptoms or ischemic electrocardiographic

TABLE 15–1 Predictive Value of Stress Nuclear Myocardial Perfusion Imaging in Patients Presenting with Unstable Angina

			Cardiac Death or MI		
Study (Year)	**No. of Patients**	**Follow-Up (mo)**	**RD, *N/n* (%)**	**No RD**	**Normal Study**
Madsen et al (1988)[63]	158	14	6/29 (21%)	4/129 (3%)	2/97 (2%)
Brown (1991)[65]	52	39	6/23 (26%)	1/29 (3%)	0/15 (0%)
Stratmann et al (1995)[66]	126	12	10/40 (25%)	1/86 (1%)	1/52 (2%)
			Annualized Cardiac Death or MI Rate (%/yr)		
Madsen et al (1988)[63]			18	2.6	1.8
Brown (1991)[65]			8	0.9	0
Stratmann et al (1995)[66]			25	1.0	1.9
Weighted average	336		19	1.7	1.6

RD, reversible defect.

changes, an abnormal stress MPI was associated with a sevenfold increase in the annual cardiac death or MI rate compared with patients with normal stress MPI (12.5% versus 1.7%; $P = .02$).[69]

As with unstable angina patients, the heterogeneity of NSTEMI patients suggests that a routine indiscriminate nonselective approach of invasive procedures and interventions may not lead to a better outcome compared with a selective approach guided by a technique capable of identifying low- and high-risk patient subgroups.

Selective Versus Nonselective Invasive Approach to Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

The TIMI IIIB trial examined the effect of thrombolysis and the possible benefit of an early nonselective invasive strategy in 1473 patients with unstable angina or non–Q-wave MI.[70] Thrombolysis was harmful in this cohort, with a higher incidence of fatal and nonfatal MI (7.4%) compared with placebo (4.9%; $P < .05$). More germane to the current discussion, the study also randomized patients to early cardiac catheterization followed by anatomy-guided revascularization or to a conservative strategy of selective catheterization and revascularization in response to spontaneous ischemia or ischemia provoked on a predischarge submaximal exercise ^{201}Tl study. There was no difference in the primary end points of death, nonfatal MI, or a positive 6-week exercise test in the invasive or conservative subgroups ($P = .33$ to $.78$), and no difference in rates of death or MI at 1 year.[71] As in the TIMI IIB trial, a nonselective invasive approach to this ACS cohort did not lead to a better outcome. The nonselective strategy was associated with a less efficient use of expensive medical resources. By design, almost all the patients in the invasive group received cardiac catheterization (98%), but only 61% underwent coronary revascularization. Coronary angiography was performed in about 40% of patients without leading to an intervention. In the selective conservative subgroup, cardiac catheterization was performed in 64% of patients because of spontaneous or provoked ischemia; 77% of this group underwent revascularization. Only 15% of the overall conservative group underwent angiography without revascularization. The use of invasive procedures to define who should undergo coronary revascularization was more efficient with a selective ischemia-guided approach.

The VANQWISH (Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital) trial results were more striking.[72] Similar to the TIMI IIIB trial, 920 patients with non–Q-wave MI were randomized to a nonselective invasive strategy or to a conservative strategy of selective catheterization with recurrent chest pain or ischemia on stress ^{201}Tl imaging. In this trial, death or MI was greater in the nonselective invasive group at 1 month and 1 year ($P < .05$), although this was no longer statistically significant at 2 years. The ischemia-guided conservative patients without angiography had a low 30-day death rate (1%) comparable to the rate with angioplasty (1.3%), indicating that stress MPI could identify low-risk patients who would not benefit from intervention, even when intervention could be performed with a low complication rate. As with the TIMI IIIB trial, the resource use was far more efficient in the selective ischemia-guided cohort. Although angioplasty was performed in 96% of the invasive group, only 44% underwent revascularization. More than half of this subgroup underwent angiography without the information leading to revascularization. In contrast, only 15% of the ischemia-guided conservative cohort went to the catheterization laboratory without going on to revascularization.

One of the criticisms of the VANQWISH trial is the high mortality rate in the invasive arm patients who had coronary artery bypass surgery. Limitations of the TIMI II/IIIB and VANQWISH trials are that the trials were performed before the introduction of glycoprotein IIb/IIIa platelet inhibitors and the use of intracoronary stents, which conceivably improved the outcome of an invasive approach. These issues were addressed in the TACTICS-TIMI 18 trial.[73] A total of 2220 patients with unstable angina or NSTEMI were treated with glycoprotein IIb/IIIa inhibitors and randomized to the usual nonselective invasive approach (using stents when clinically indicated) versus an ischemia-guided conservative strategy based on spontaneous ischemia or the results of exercise imaging. In the overall cohort, outcome (death, MI, or rehospitalization for ACS) was better in the invasive subgroup. This benefit was confined, however, to the high-risk subgroup of patients with ST-segment changes on presentation or a serum troponin level higher than 0.01 mg/mL. In the approximately 60% of patients without these markers, there was no difference in outcome based on strategy. The invasive strategy showed a borderline benefit in an intermediate-risk subgroup based on TIMI risk score.

The TACTICS-TIMI 18 trial suggests that a nonselective invasive approach may have an advantage in high-risk patients. In low-risk patients, an ischemia-guided selective approach to coronary angiography and intervention seems to lead to an outcome at least as good as that of a nonselective strategy. A reanalysis of the TIMI IIIB trial has confirmed this principle.[74] When TIMI IIIB patients were stratified clinically by age, electrocardiographic changes, enzyme levels, and symptoms, benefit of a nonselective invasive approach at 42 days was seen only in the high-risk or very high-risk

subgroup. Such patients accounted for only 19% of the total group, however. There was a trend for a superior outcome with a selective ischemia-guided conservative approach in low-risk subgroups. By 1 year, the interaction between clinical risk and strategy was not statistically significant.

The FRISC II trial also compared an invasive and conservative approach in patients presenting with ACS and found an outcome advantage for the invasive strategy (9.4% death or MI versus 12.1% in the conservative group at 6 months).[75] A threshold of higher than 3 mm of ST-segment depression on stress testing before referring to angiography and revascularization was used. As a result, although the cohort was fairly high risk (57% with multivessel or left main disease, 58% with elevated troponin, 22% with prior MI, 46% with ST-segment abnormalities on presentation), only 10% of the conservative group was referred for early angiography, and only 9% underwent revascularization. When the same criteria for cardiac catheterization were applied to the VANQWISH cohort, the FRISC II criteria identified only half of patients found to have surgical CAD by the VANQWISH criteria.[76] The FRISC II trial thus does not address the role of a selective approach to angiography in the ACS patient based on using modern, sensitive stress nuclear MPI imaging to identify patients at risk for cardiac events.

The experience at Baylor Methodist Hospital with 2414 patients presenting with unstable angina was similar to their previously described experience with acute MI.[45] Most patients (almost 80%) had cardiac catheterization as their first diagnostic test, and most had revascularization (see Fig. 15-7). Only 5% were first screened with stress nuclear MPI; an additional 4% underwent MPI after catheterization. Similar to acute MI patients, the invasive approach did not lead to a better outcome in patients admitted with unstable angina. The in-hospital mortality for patients undergoing catheterization without nuclear MPI was 5% compared with 1% in patients who were evaluated with MPI ($P < .001$; see Fig. 15-7). The mortality was 6% in revascularized patients evaluated only with angiography compared with 0% in patients undergoing nuclear MPI before revascularization ($P < .001$). Although this was not a randomized trial, the difference in outcome between the approaches could not be explained by a higher risk clinical profile in the catheterization group. There was a trend toward a higher incidence of heart failure in the nuclear MPI group ($P = .06$). This study suggests that using nuclear MPI to choose patients for angiography and revascularization may lead to a better outcome, and sounds another note of caution about a routine nonselective invasive approach.

Suppression of Ischemia Detected by Stress Myocardial Infarction and Outcome

Although it has been generally assumed that coronary revascularization is more effective than medical treatment in suppressing stress-induced ischemia, compelling data show that both are comparably effective and, most importantly, that outcome is dependent on the degree of suppression, regardless of mechanism. In a 44-patient pilot study of survivors of acute MI, Dakik and colleagues examined changes in serial adenosine stress MPI and outcomes when randomized to optimized medical treatment versus coronary intervention.[77] They found that the degree of ischemia suppression and the number of patients achieving a more than 9% reduction in ischemia was identical in medically treated versus intervention patients. Importantly, the cardiac event rate was very low in patients with a more than 9% reduction of ischemia regardless of type of treatment compared with patients without such suppression (Fig. 15-8). These observations were confirmed in the larger INSPIRE trial involving 205 survivors of acute MI with high-risk stress MPI (>20% LV total defect size, >10% LV reversible defects) who were similarly randomized to optimized medical treatment or coronary revascularization.[78] The absolute reduction in ischemic burden was very similar in the medically treated (15% ± 9%) versus revascularization (16.2% ± 9%) patients. The percentage of patients achieving a more than 9% absolute reduction of ischemia was also very similar (80% vs. 81%; $P = .76$, respectively). In addition, cardiac death or MI rates were not different in the two groups (8% vs. 7%; P = not significant). Importantly, although each treatment cohort showed significant reduction in ischemic burden, the individual responses within these subgroups were variable. Because outcome is dependent on the degree of ischemic burden reduction, it is crucial to document such reduction by repeating stress MPI after treatment.

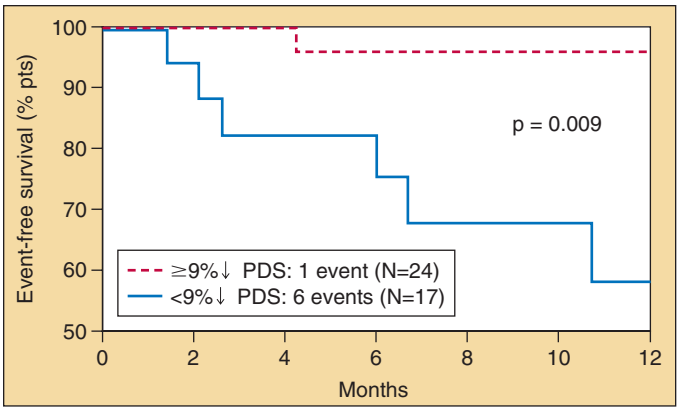

FIGURE 15–8 Event-free survivial as a function of degree of ischemia suppression. Patients with a reduction in perfusion defect size (PDS) of >9% by coronary intervention or medical treatment had a significantly better survival than patients with less than 9% suppression. *(From Dakik HA, Kleiman NS, Farmer JA, et al: Intensive medical therapy versus coronary angioplasty for suppression of myocardial ischemia in survivors of acute myocardial infarction: A prospective randomized pilot study. Circulation 1998;98:2017-2023.)*

Acute Transient Apical Ballooning (Takotsubo Cardiomyopathy) and Nuclear Cardiac Imaging

Transient LV apical ballooning (Takotsubo cardiomyopathy) can mimic acute MI because it is associated with transient ST-segment changes suggestive of ischemia but is associated with angiographically normal coronaries. The presentation is often associated with marked elevations in plasma catecholamine levels.[79] Ito and associates[80] have examined serial resting MPI in 10 patients with Takotsubo cardiomyopathy. All patients had normal angiographic coronaries but resting MPI showed apical perfusion defects acutely that resolved on repeat imaging at 3 to 9 days and 1 month later. This improvement in perfusion was paralleled by improvement in wall motion. The authors speculated that impaired microcirculation was a causative factor. At 5 days after presentation, ^{123}Imaging with Iodine-123-beta-methyl-iodophenyl-pentadecanoic (I^{123} BMIPP), a tracer for myocardial fatty acid, showed more extensive defects than resting ^{201}Tl-MPI, consistent with metabolic changes caused by an ischemic insult. The ^{123}I-BMIPP defects resolved with serial imaging over 30 days.[81] Burgdorf and coworkers[82] examined perfusion and cardiac adrenergic function with resting MPI and ^{123}I-metaiodobenzylguanidine (MIBG) imaging in 10 patients with Takotsubo cardiomyopathy. They found decreased apical MIBG cardiac uptake and rapid washout consistent with alterations in cardiac presynaptic

sympathetic neurotransmission at 3 to 9 days, despite normal myocardial perfusion and improving LV contractile function at this subacute stage. The rapid washout of MIBG was consistent with markedly elevated levels of circulating catecholamines documented in this cohort. Similar findings were reported by Uchida and colleagues[83] with enhanced MIBG washout and elevated norepinephrine levels in patients with this syndrome who showed decreased ^{123}I-BMIPP uptake consistent with an ischemic insult. Such neurohumeral abnormalities may play an important role in the pathophysiologic mechanism of this condition.

EMERGENCY DEPARTMENT TRIAGE OF PATIENTS PRESENTING WITH CHEST PAIN

The identification of ACS in patients who present to the emergency department with nonspecific symptoms and nonischemic ECG changes is problematic because, although the true incidence is low, the clinical risk associated with ACS is high and can be reduced with effective treatment when the diagnosis is made correctly. Consequently, physicians tend to have a low threshold for admission of such patients, leading to higher costs, although most patients are discharged later without the diagnosis of MI or unstable angina.[84] Despite the best clinical judgment of physicians, the missed MI rate ranges from 2% to 10%.[85-90] This basic dilemma results from the intrinsic nonspecific nature of the presenting complaint and the low sensitivity and specificity of the ECG.[91-93] Clinical risk factors have been shown to be of little benefit because of their low specificity.[94-98] Serum biomarkers of myocardial imaging (troponin, creatine kinase, MB fraction) are very helpful to diagnose acute MI when sampled serially over time, but initial levels at the time of emergency department presentation have a low sensitivity for acute MI. Acute injection of a radionuclide MPI agent at the time of presentation, followed by early imaging, offers a possible technique for detecting myocardial ischemia at the time of emergency department presentation. Such an approach potentially can improve sensitivity and specificity for detecting patients at risk for cardiac events, leading to a more cost-effective triage of the problematic patient.

Early Data

In 1976, Wackers and colleagues[99] showed that a single injection of ^{201}Tl had a high sensitivity for detecting patients with acute MI that appeared to be time-dependent: The sensitivity was 100% when injected within 6 hours, 96% when injected within 24 hours, and 79% when injected after 48 hours. Serial imaging in individual patients showed a reduction in the size of the defect over 24 hours, suggesting that early initial imaging reflected infarct plus ischemia that resolved with time. Early studies showed a much lower sensitivity for detecting patients with unstable angina compared with patients with acute MI.[100] Although no patient presenting with acute MI had a normal imaging study, half the patients presenting with unstable angina had normal imaging. This finding probably was related to the wide time frame of tracer injection after presentation to the emergency department (10 hours), because other studies have shown the sensitivity of rest ^{201}Tl imaging to be time-dependent in patients presenting with unstable angina. Wackers and associates[101] found the sensitivity for unstable angina was 84% when patients were injected within 6 hours of chest pain compared with 19% when injected 12 to 18 hours after chest pain. The frequency of ischemia seen on rest ^{201}Tl imaging seems to be related to the type of presenting clinical syndrome.[102] After a rest injection of ^{201}Tl, serial initial and delayed imaging showed that 19 of 19 patients (100%) presenting with crescendo exertional unstable angina had transient defects compared with only 3 of 12 (25%) with rest angina alone and 4 of 34 (12%) with stable angina ($P < .0001$). The high frequency of resting ischemia occurred in the crescendo angina group, even though no patient had chest pain within 4 hours of injection.

These early studies, which all used planar imaging, showed the potential for using this technique to identify high-risk and low-risk patients. Wackers and coworkers[101] showed that rest ^{201}Tl injection within 18 hours of chest pain could identify 76% of patients who went on to have a complicated hospital course. Van der Wieken and colleagues[103] showed that 99% of patients presenting with chest pain and a nondiagnostic ECG who had normal ^{201}Tl rest imaging studies within 12 hours of presentation did not go on to develop an acute MI.

Technetium-99m–Based Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

The introduction of ^{99m}Tc-based perfusion agents (sestamibi and tetrofosmin) has improved the potential of rest MPI for risk stratification of patients with chest pain presenting to the emergency department. The improved dosimetry makes the agents more suitable for SPECT, with improved sensitivity for detecting ischemia and infarction, especially in the left circumflex artery territory.[104-108] The superior dosimetry also makes the agents suitable for evaluation of ventricular function, which can improve the predictive value of the test.[109,110] Finally, because (in contrast to ^{201}Tl) the myocardial distribution remains stable over time, injection of a ^{99m}Tc-based tracer does not need to be closely linked in time with imaging, facilitating the logistics of using this technique.[111-113] Patients can be injected rapidly in the emergency department, and imaging can be arranged when convenient without loss of diagnostic information.

Bilodeau and associates[114] have evaluated the sensitivity of SPECT imaging after an injection of ^{99m}Tc-sestamibi at rest during chest pain and after resolution in 45 patients presenting to the emergency department without known CAD. The sensitivity for detection of CAD was 96% when injection occurred during chest pain and 65% when injection occurred during a pain-free period. This sensitivity was significantly higher than for 12-lead electrocardiography (35% to 38%). The specificity for resting MPI was also fairly high, 79% with chest pain and 84% without. The location of the perfusion defect corresponded with the most severe coronary lesion on angiography in 88% of patients, and the size of the perfusion defect correlated with the extent of CAD. Rest ^{99m}Tc-sestamibi SPECT imaging showed high promise as a tool for screening patients on presentation to the emergency department with chest pain of unclear origin. Subsequent studies confirmed its potential value.

Varetto and coworkers[115] have examined the predictive value of rest ^{99m}Tc-sestamibi SPECT imaging in a series of 64 patients presenting to the emergency department with chest pain but nondiagnostic ECG. None of the 34 patients with normal imaging subsequently were found to have CAD, whereas 27 of 30 patients (90%) with perfusion defects were determined to have unstable angina or were ruled in for acute MI. Of the 14 patients with unstable angina, 11 had defects despite being injected 2 to 8 hours (mean, 5 hours) after the rest pain had resolved. Repeat imaging 12 to 24 hours later showed complete resolution of the defects. Injection of ^{99m}Tc-sestamibi at the time of presentation seemed to be highly sensitive (100%) and specific (92%) for detecting patients with CAD, even if injection were done after chest pain had resolved for several hours. Because the defects had normalized by 24 to 48 hours, however, there was a gradual

resolution of ischemia; the rate probably reflects the severity of the ischemic insult. It would be expected that the sensitivity for detecting ischemia would be greatest if injection were made when the chest pain was still present.

Hilton and colleagues[116] took the next step and evaluated the ability of rest ^{99m}Tc-sestamibi SPECT imaging in the emergency department to predict subsequent cardiac events in 102 patients with anginal symptoms but normal or nondiagnostic ECGs. All patients in this series were injected while still having chest pain. Patients without defects had a cardiac event rate of only 1%, whereas 71% of patients with definite perfusion defects had cardiac events. Equivocal imaging results were associated with an intermediate risk (13%). The ability to separate low-risk from high-risk patients was superior for rest ^{99m}Tc-sestamibi imaging compared with clinical or electrocardiographic data (Figs. 15-9 and 15-10).

Other studies using either ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin subsequently reported similar findings of a high sensitivity for detecting patients at risk for acute MI and other cardiac events.[117-120] This translates into a high negative predictive value for such cardiac events (Table 15-2). Rest imaging in the emergency department can be a helpful tool for determining whether a patient can be sent home safely for additional outpatient evaluation. A comprehensive goal-driven strategy that integrates clinical risk and acute rest ^{99m}Tc-sestamibi MPI was introduced at the Medical College of Virginia (Fig. 15-11).[117,121] Levels 1 and 2 patients (high to very high risk) were presumed to have ischemia and were admitted. Levels 3 and 4 patients (low to moderate risk) had ^{99m}Tc-sestamibi imaging–guided management, whereas level 5 patients (very low risk) were sent home without additional testing. Among 438 patients undergoing acute imaging (level

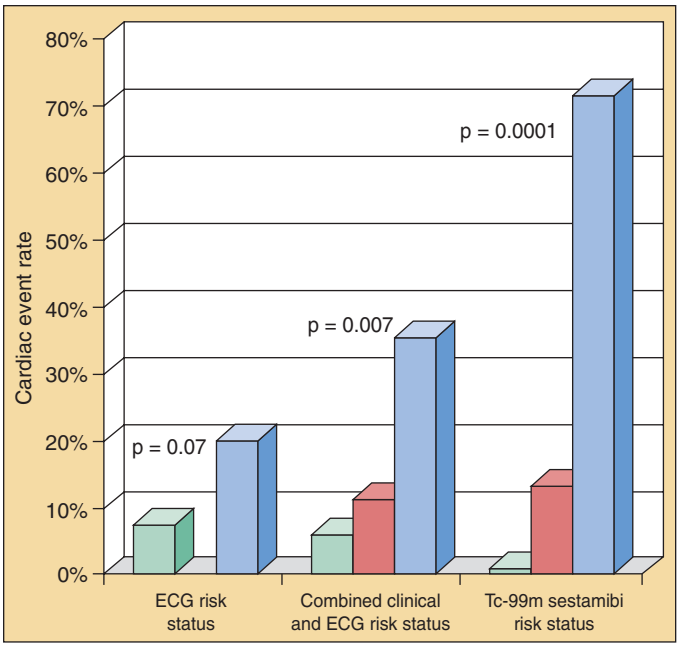

FIGURE 15–9 Risk of cardiac events in patients presenting to the emergency department with chest pain and nondiagnostic ECG, using electrocardiographic results versus electrocardiographic plus clinical data or acute ^{99m}Tc-sestamibi imaging results. The ability to separate low-risk and high-risk subgroups was better with ^{99m}Tc-sestamibi imaging than with the ECG alone or with clinical data. *(From Hilton TC, Thompson RC, Williams HJ, et al: Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. J Am Coll Cardiol 1994;23:1016-1022.)*

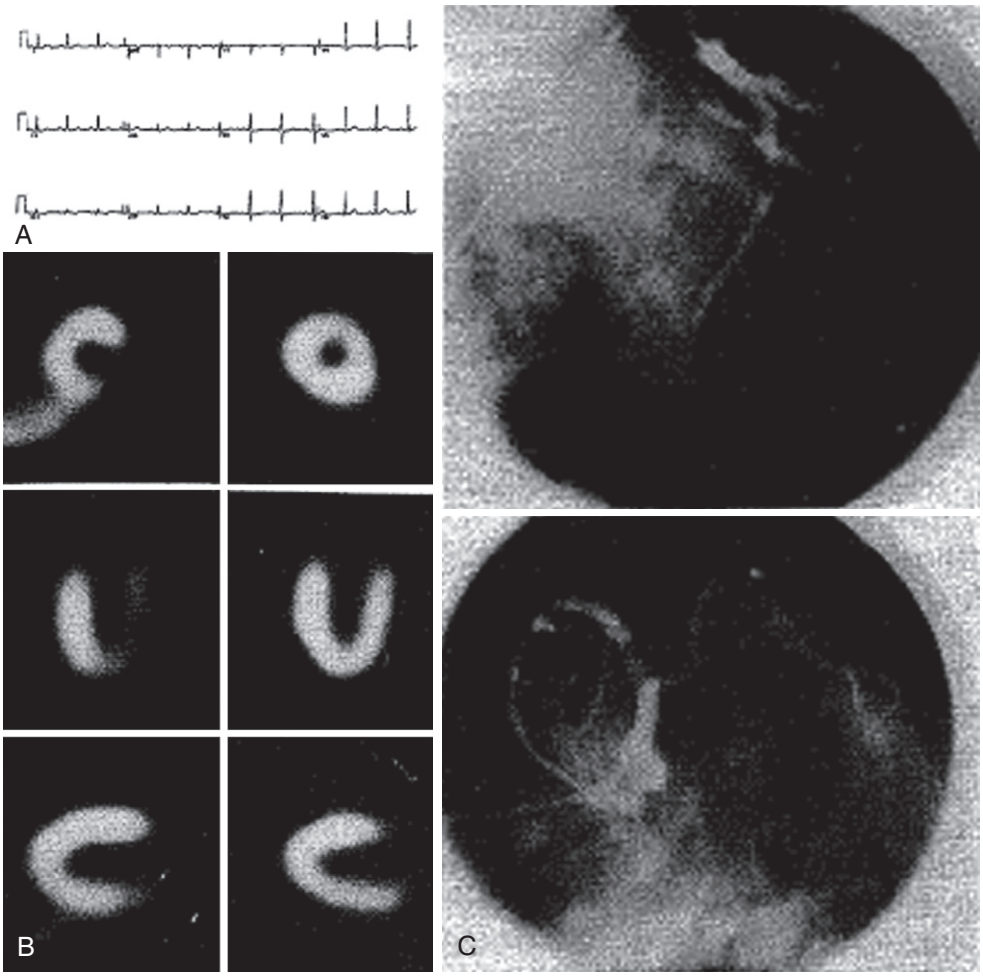

FIGURE 15–10 **A,** A 60-year-old man presenting with chest pain but nonspecific electrocardiogram. **B,** Acute ^{99m}Tc-sestamibi imaging in the short-axis *(top)*, horizontal long-axis *(middle)*, and vertical long-axis *(bottom)* projection shows a perfusion defect in the lateral wall *(left column)*. **C,** Coronary angiography showed a high-grade lesion in the left circumflex artery on right anterior oblique *(upper)* and left anterior oblique *(lower)* projections. After coronary angioplasty, repeat ^{99m}Tc-sestamibi imaging showed resolution of the perfusion defect (**B,** *right column*). *(From Hilton TC, Thompson RC, Williams HJ, et al: Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. J Am Coll Cardiol 1994;23:1016-1022.)*

TABLE 15–2 Negative Predictive Value of Normal Rest ^{99m}Tc-Sestamibi Imaging*

Study (Year)	No. of Patients	Normal Patients (% of Total)	NPV (%)
Bilodeau et al (1991)[114]	45	26 (58%)	94
Varetto et al (1993)[115]	64	34 (53%)	100
Hilton et al (1994)[116]	102	70 (69%)	99
Tatum et al (1997)[117]	438	338 (77%)	100
Kontos et al (1997)[118]	532	361 (68%)	99
Heller et al (1998)[119]	357	204 (57%)	99
Kontos et al (1998)[120]	620	379 (61%)	99

*In patients who present to the emergency department with chest pain and nondiagnostic electrocardiogram.
NPV, negative predictive value.

3 or 4), 338 patients had normal imaging results. Over the next year, no patient with normal imaging had an acute MI, and only 10 (3%) underwent coronary revascularization. In contrast, of the 100 patients with resting perfusion defects, 42 developed an ischemic cardiac event, including 20 (20%) deaths or MIs. Acute rest imaging can play an important role in identifying low-risk patients who can be sent home safely and high-risk patients who require additional study.

Timing of Injection

As noted, sensitivity for detecting myocardial ischemia using rest ^{99m}Tc-sestamibi MPI diminishes over time if the ischemic insult resolves. Sensitivity is greatest, over 90%, if the tracer is injected while the patient is still having chest pain, even without electrocardiographic changes.[114] Injection early after chest pain has resolved, within 2 to 8 hours, can still detect patients with CAD up to 79% of the time.[115] It is likely that the duration of time following cessation of chest pain when resting ^{99m}Tc-sestamibi MPI will still show perfusion defects is related to the extent and severity of the ischemic insult.

^{123}I-BMIPP may have unique applications in the emergency department setting.[122] Because ischemia changes the myocardial metabolic substrate from fatty acid to glucose, such metabolic changes may persist longer in duration than reduction in perfusion. Therefore, an imaging agent such as ^{123}I-BMIPP may show reductions in uptake following myocardial ischemia that persist when myocardial perfusion has returned to normal, and therefore may be more valuable in the emergency department setting. In a series of 111 patients with acute chest pain syndromes that had resolved 1 to 5 days prior to presentation, ^{123}I-BMIPP imaging had a sensitivity of 74% for the detection of CAD compared with only 38% for ^{99m}Tc-sestamibi MPI (I-18). Clearly, more data are needed to establish the usefulness of ^{123}I-BMIPP imaging in the emergency department setting.

Cost-Effectiveness

Several studies have evaluated the potential cost savings associated with the use of acute emergency department imaging to guide management. In a series of patients presenting to the emergency department with unexplained chest pain, Weissman and associates[123] have compared the costs of acute ^{99m}Tc-sestamibi imaging plus the costs of altered management based on imaging results with the costs of managing patients before imaging was introduced. Using acute imaging to guide management, costs were reduced by almost $800 per patient, and no patient sent home on the basis of normal

ACT STRATEGY FOR CHEST PAIN EVALUATION AND TRIAGE
RISK BASED AND GOAL-DRIVEN

Level assignment based on CP character, history, and initial ECG

Level	Risk	Goal	Disposition	Diagnostic strategy
1	Very high	Intervention	Treat and admit CICU	Presenting ECG
2	High	Intervention	Admit CICU	Serial ECGs and markers
3	Moderate	R/in ACS	"Fast track"	Serial ECGs acute perfusion imaging
4	Low	Risk stratification	ED workup	Acute perfusion imaging
5	Very low	Alternate diagnosis	Home	Appropriate referral

Risk ↑

Acute cardiac team (ACT) Medical College of Virginia hospitals/VCU/Richmond, Va.

FIGURE 15–11 Strategy at Medical College of Virginia Hospitals for chest pain evaluation and triage in the emergency department based on assessment of clinical risk and integration of acute nuclear perfusion imaging into decision analysis for low-risk and moderate-risk patients. CICU, cardiac intensive care unit; CP, chest pain; ED, emergency department. *(From Tatum JL, Jesse RL: Emergency department triage and imaging of patients with acute chest pain. In Zaret BL, Beller GA [eds]: Nuclear Cardiology: State of the Art and Future Directions, 2nd ed. St. Louis, Mosby, 1999, pp 468-489.)*

imaging had an adverse event. Similarly, Radensky and colleagues[124] have compared a strategy of using acute ^{99m}Tc-sestamibi imaging to guide admission (positive scan) or discharge (normal scan) with a strategy that used only clinical and electrocardiographic data. They found that costs were reduced by more than $1000 per patient by using acute imaging to guide triage of patients. The cost savings were the result of a much lower admission rate for patients who did not have cardiac events with the imaging-guided strategy (14%) versus the clinical and electrocardiographic data–guided strategy (54%). At the same time, the sensitivity for detecting patients at risk for cardiac events using imaging was not compromised—94% versus 88% for the clinical and electrocardiographic data strategy.

Stowers and coworkers[125] have compared the resource use and outcome of intermediate-risk patients presenting to the emergency department with chest pain and no electrocardiographic evidence of acute ischemia who were randomized to conventional or ^{99m}Tc-sestamibi MPI-guided management. In the MPI-guided group, patients were treated according to a predefined protocol based on imaging results. Patients with a positive scan underwent cardiac catheterization, whereas patients with a negative scan underwent exercise treadmill testing. Patients in the conventional treatment group were managed at their physician's discretion. Investigators found that although in-hospital and 30-day event rates were similar, MPI-guided patients had $1843 less median in-hospital costs and hospitalizations 2 days shorter than conventionally treated patients. Cost savings were related to a lower rate of cardiac catheterization and the shorter stay.

The contribution of rest MPI to emergency room triage decision was examined in a randomized trial involving 2475 patients presenting with possible acute coronary syndromes but a nondiagnostic or normal ECG.[126] Patients randomized to MPI strategy had fewer admissions (47.5% vs. 56.1%; $P < .001$) but there was no difference in outcome compared with the usual strategy. One patient in each group who was subsequently determined to have acute coronary syndrome (0.1%) was sent home. Thus, incorporating MPI into emergency department decision making reduced unnecessary admissions without reducing appropriate admissions for

acute ischemia. A subsequent report from this group found a similar reduction in unnecessary admissions in the subgroup with diabetes mellitus, although the overall admission rate was higher.[127]

Kontos and colleagues[128] have reported the cost impact of implementing the previously described Medical College of Virginia emergency department algorithm incorporating MPI. They found that the new strategy with MPI reduced costs across the board for each level of risk and was associated with a lower angiography rate and shorter length of stay.

Acute rest MPI in the emergency department can be an effective diagnostic and prognostic tool that can help physicians make management decisions for patients with undefined chest pain syndromes, leading to cost savings without compromising patient outcomes. This tool should become increasingly attractive as pressures for cost containment increase at the same time that usage of emergency department resources grows.

CONCLUSIONS

Nuclear cardiology techniques have powerful diagnostic and prognostic value that can help physicians make timely and rational management decisions across a wide spectrum of patients with ACS. By distinguishing the low-risk patient who would not benefit from further testing or intervention from the high-risk patient who would benefit, nuclear techniques can lead to cost-effective use of medical resources and to optimizing patient outcome. They also can help evaluate the presence of viable myocardium in patients with left ventricular dysfunction as an additional guide toward revascularization.

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CHAPTER 16

Multislice Computed Tomography in Acute Coronary Syndromes

Pim J. de Feyter and Koen Nieman

High-quality, noninvasive coronary imaging requires high spatial resolution and a high acquisition speed because of the small size, tortuous course, and continuous motion of the coronary arteries. Computed tomography (CT) has emerged as the most effective technique to visualize the coronary arteries noninvasively. Electron beam computed tomography (EBCT), which was introduced in the mid-1980s, is a high-speed CT scanner designed for cardiac imaging. Although mostly used for the detection and quantification of coronary calcium, EBCT also allows contrast-enhanced coronary angiography. Since the early 2000s, multislice computed tomography (MSCT) scanners with cardiac imaging capabilities have been developed. MSCT scanners can be used to detect and quantify coronary calcium, but were primarily developed to image the coronary arteries. Current state-of-the-art scanners are equipped with 64 or more detector rows. Dual-source scanners are available that allow even faster acquisition of images. In this chapter, we will discuss the value of coronary calcium scoring and total coronary plaque burden as assessed by CT, and the role of CT coronary angiography in the evaluation of patients presenting with acute coronary syndromes.

PREDICTION OF ADVERSE CARDIOVASCULAR EVENTS

Computed Tomography Coronary Calcium Scoring

Coronary calcium is easily identified by CT because the roentgenographic attenuation of calcium is much higher compared with that of the surrounding tissues (Fig. 16-1). Histologic studies have shown that a CT tissue density of greater than or equal to 130 HU is highly correlated with calcified coronary plaques.[1] The presence of coronary calcium is evidence of the presence of coronary atherosclerosis. The extent of coronary calcium correlates with the overall atherosclerotic plaque burden (i.e., presence of calcific and noncalcific atherosclerosis), although the calcific plaques constitute only 20% of the total coronary plaque burden.[1-7] A large amount of coronary calcium is associated with an increased likelihood of vulnerable plaque present somewhere in the coronary tree, but does not identify the site of a specific vulnerable plaque. Absence of coronary calcium does not exclude coronary atherosclerosis, including the presence of a high-risk plaque, but its presence is very unlikely.

The amount of coronary calcium can be quantified in different ways. The most widely used method is the Agatston calcium score, based on the peak CT density (>130 HU) and the area of the calcific plaque (≥1 mm^2).[8] For each calcified lesion, the area is multiplied by a factor determined by the peak CT density: 1 for a peak density of 130 to 199 HU, 2 for 200 to 299 HU, 3 for 300 to 399 HU, and 4 for 400 HU or more. By adding up the individual plaque scores, the total Agatston score can be determined. Several large-scale long-term follow-up studies have assessed the value of calcium scoring to predict cardiovascular events in high-risk asymptomatic populations (Table 16-1).[9-15] A coronary calcium score of 0 is associated with a very low risk (<0.4% annual risk) of the occurrence of an adverse cardiovascular event and there is a strong direct relationship between the magnitude of the calcium score and the occurrence of adverse events (Tables 16-2 and 16-3).

A meta-analysis of the prognostic value of coronary calcium was recently performed (Tables 16-4 and 16-5).[16] Overall, the relative risk ratio of having calcium compared with the absence of calcium was 4.3 (95% confidence interval [CI], 3.5 to 5.2) and the relative risk ratios revealed a close relationship with higher calcium scores associated with higher event rates and higher relative risk ratios.

It is important to note that the predictive value of the calcium score was retained after correction for age and gender, because calcium deposition increases with age and is higher in men. These large-scale studies also indicated that the calcium score had an incremental predictive value beyond traditional risk factors.[9,10] CT coronary calcium screening is generally not recommended for asymptomatic individuals

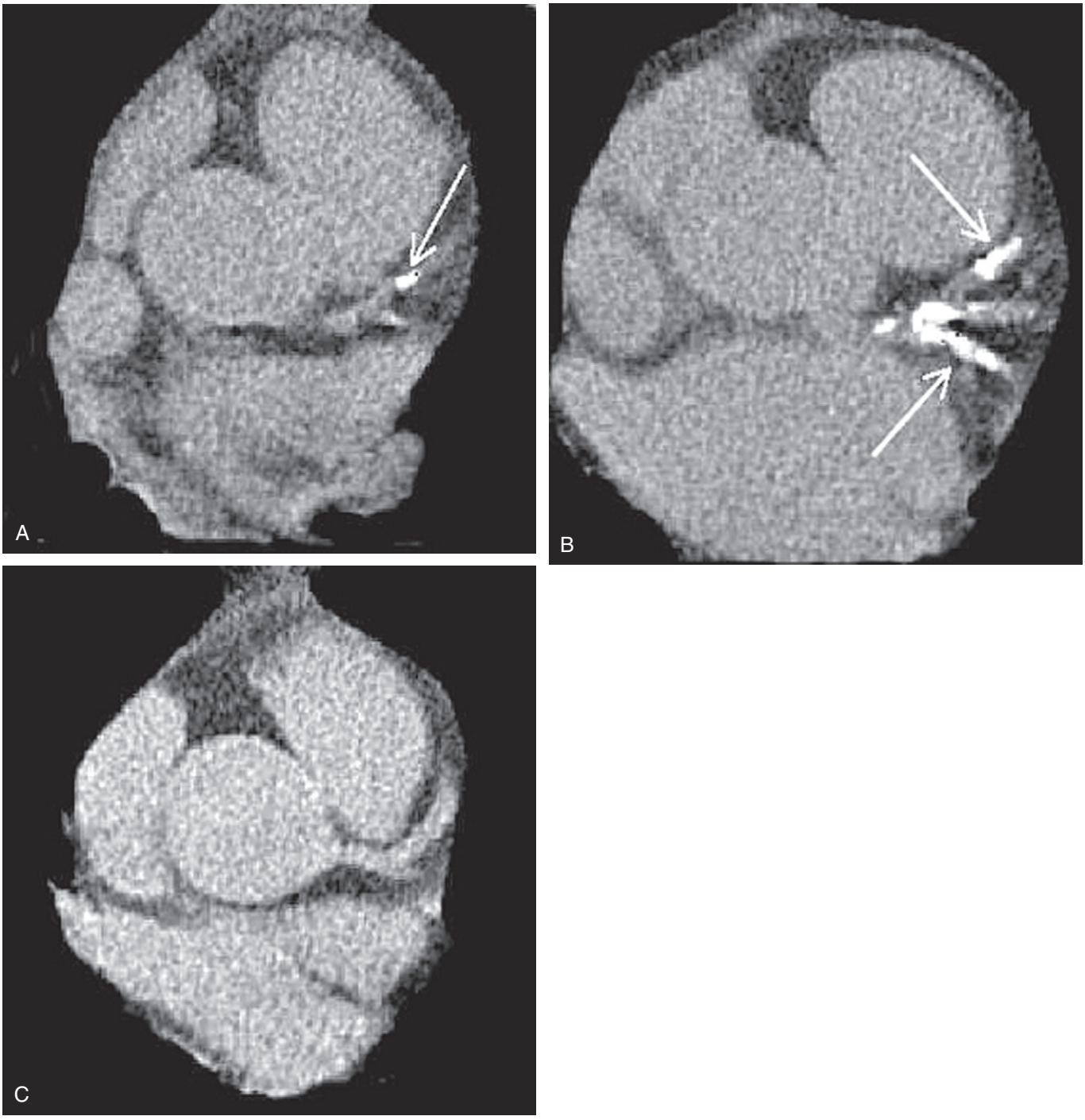

FIGURE 16–1 **A,** a small calcific plaque in LAD; **B,** extensive calcific plaque in left main LAD and LCx; **C,** no presence of calcium. High-density calcific plaques visible as bright dots (*arrows*). LAD, left anterior descending artery; LCx, left cireumflex coronary artery.

at low or high risk of cardiovascular disease. Calcium screening may be useful for intermediate-risk individuals in whom a low calcium score suggests an actual low risk, whereas those with a high calcium score (>400) should be reclassified to high risk, justifying intensive modification of risk factors.[16]

Computed Tomography Coronary Imaging: Total Plaque Burden

The extent of obstructive coronary artery disease (one-, two-, or three-vessel disease or left main disease) determined by invasive coronary angiography predicts subsequent patient outcome.[17] It is expected that assessment of coronary obstruction by noninvasive CT angiography has a similar predictive value. Pundziute and colleagues[18] were the first to report the prognostic value of CT coronary imaging in 100 symptomatic patients to predict the combined end points of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and revascularization. The presence of CT obstructive and nonobstructive disease was associated with a 30% adverse event rate at 1 year, whereas the absence of CT disease was associated with a 0% event rate. However, most adverse events were revascularizations.

TABLE 16–1 Computed Tomography Calcium Score Prediction of Cardiovascular Events

Study (Year)	No. of Patients	Age (yr)	Follow-up (yr)	Completeness Follow-Up (%)	Predictive Calcium Score	Prevalence NP*	Comparative Group Calcium Score (Prevalence)†	End Point (NP)	RR
Shaw et al (2003)[9]	10,377	53 ± 0.1	5	100	>40	935	≤10 (5946)	All-cause mortality (249)	6.2
Greenland et al (2004)[10]	1312	66 ± 8	7	88	>300	221	0 (316)	Cardiac death/MI (84)	3.9
Arad et al (2005)[11]	4613	59 ± 6	4.3	94	≥100	1136	<100 (3477)	Cardiac death or MI (119)	9.2
Taylor et al (2005)[12]	1627	43 ± 3	3	99	>0	364	0 (1363)	Death or MI UA (9)	11.8
Vliegenthart et al (2005)[13]	1795	71 ± 6	3.3	99	>1000	196	0-100 (905)	Death/MI (40)	8.1
LaMonte et al (2005)[14]	6835 (men) 3911 (women)	54 ± 10	3.5	70	>250 >113	1380 376	0 (2692) 0 (2780)	Cardiac death or MI (81) idem	8.7‡ 6.3‡
Budoff et al (2007)[15]	25,253	56 ± 11	6.8	100	>10	14,207	0 (11,046)	All-cause mortality	1.7

*Number of patients with predictive calcium score.
†Number of patients in this group with defined calcium score as comparison.
‡Calculated per 1000 person-years.
RR, relative risk; UA, unstable angina.

TABLE 16–2 Prognostic Value of Coronary Calcium Score for All-Cause Mortality*

Calcium Score	No. of Patients (%)	All-Cause Death (%)	RRR	RRR (Adjusted Risk Factors)*
≤10	5946 (57)	1.0 (62)	—	—
11-100	2044 (20)	2.6 (53)	2.5	1.7
101-400	1432 (14)	3.8 (54)	3.6	1.8
401-1000	623 (6.0)	6.3 (39)	6.2	2.6
>1000	332 (3.2)	12.3 (41)	12.3	4.0

*10,377 asymptomatic individuals; total deaths = 2.4% (*N* = 249).
RRR, relative risk ratio.
Data from Shaw LJ, Raggi P, Schisterman E et al: Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826-833.

TABLE 16–3 Coronary Calcification Predictive of Long-Term Prognosis*

Calcium Score	No. of Patients (%)	RRR	RRR (Adjusted Age + Risk Factors)
0	11,046 (44)	—	—
1-10	3567 (14)	2.6	1.5
11-100	5033 (20)	6.7	3.6
101-400	3177 (13)	13	3.9
401-1000	1469 (6)	23	6.2
> 1000	965 (4)	38	9.4

*25,253 asymptomatic individuals; all-cause death, 2% (*N* = 510).
RRR, relative risk ratio.
Data from Budoff MJ, Shaw LJ, Liu ST, et al: Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860-1870.

TABLE 16–4 Results of Meta-Analyses of Prognostic Value of Coronary Calcium Score

Parameter	Results
Total no. of patients	27,622
Follow-up (yr)	3-5
CHD death or MI	395
High- vs. low-risk events	
364/19,039 events	CS > 0
49/11,815 events	CS = 0
Relative risk ratio	4.3 (95% CI, 3.5-5.2)

CHD, coronary heart disease; CS, calculated score.
Data from Greenland P, Bonow RO, Brundage BH, et al; Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography: ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378-402.

Min and associates[19] have studied the predictive value of CT coronary imaging in 1127 patients 45 years or older with chest pain. All-cause death was assessed during a follow-up period of 15.3 ± 3.9 months. The overall mortality was 3.5%. A normal CT scan predicted a very low mortality rate of 0.3%. The presence, extent, and severity of coronary artery disease were significant predictors of all-cause mortality. The worst outcome occurred in patients with three-vessel disease and left main disease, demonstrating that noninvasive CT coronary angiography imparts a predictive value similar to that of invasive coronary angiography (Fig. 16-2).[17]

TABLE 16–5	Relative Risk Ratios According to Level of Risk	
Risk	**Coronary Calcium Score**	**RRR**
Average	1-112	1.9 (1.3-2.8)
Moderate	100-400	4.3 (3.1-6.1)
High	400-999	7.2 (5.2-9.9)
Very high	>1000	10.8 (4.2-27.7)

RRR, relative risk ratio.

Data from Greenland P, Bonow RO, Brundage BH, et al; Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography: ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378-402.

Computed Tomography Coronary Angiography in Patients with Acute Coronary Syndromes

The feasibility of CT coronary angiography to detect significant coronary stenoses in patients with acute coronary syndromes (ACS) was shown using 4- and 16-slice CT scanners.[20,21] The clinical value of 4- and 16-slice CT scanners was limited by the rather high rate of noninterpretability because of insufficient image quality and the need for exclusion of patients. The diagnostic performance improved with 64-slice CT technology. In 104 patients with a non–ST-elevation acute coronary syndrome, Meijboom and coworkers[22] have demonstrated that 64-slice CT coronary angiography has a high sensitivity to detect coronary stenoses and could reliably exclude significant coronary artery disease (Table 16-6). The role of CT in acute coronary syndromes has not been settled, and is limited by the fact that CT cannot replace invasive coronary angiography necessary to identify patients for immediate coronary revascularization. There is no role for CT coronary angiography in patients with ST-segment elevation myocardial infarction (STEMI), in whom immediate primary percutaneous intervention (PCI)—or, if not, possible thrombolysis—is recommended. There may be a small role for MSCT in patients with non–ST-segment elevation myocardial infarction (NSTEMI). These patients are stratified into high-, intermediate-, and low-risk profiles according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines or into high- and low-risk groups according to European Society of Cardiology (ESC) guidelines based on clinical presentation, electrocardiographic (ECG) changes, biomarkers, electrical or hemodynamic instability, and presence of diabetes mellitus.[23,24] CT coronary angiography is not recommended for high-risk groups because these patients benefit from an early invasive strategy and coronary revascularization. Low- to intermediate-risk groups may undergo initial evaluation with CT coronary angiography to exclude the presence of significant coronary artery disease, which may occur in up to 30% of patients (Fig. 16-3).[25,26] Further studies are needed to establish the role of CT coronary angiography in relation to other noninvasive functional tests (e.g., single-photon emission computed tomography [SPECT], stress echocardiography) in these low- to intermediate-risk patients.

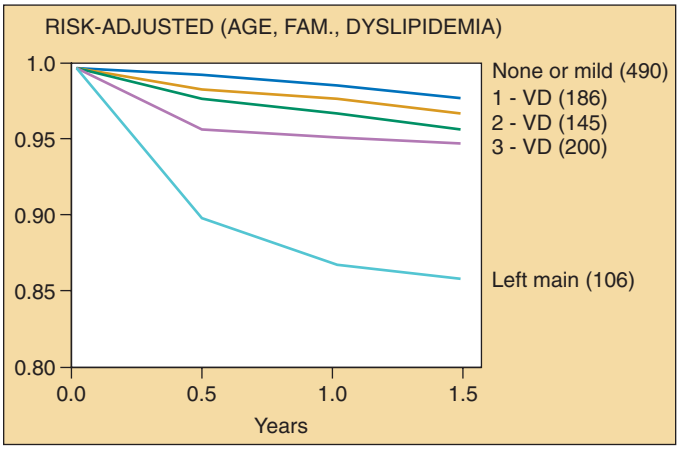

FIGURE 16–2 All-cause mortality in 1127 patients with chest pain followed for 15.3 ± 4 months. *(Adapted from Min JK, Shaw LJ, Devereux RB, et al: Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 2007;50:1161-1170.)*

TABLE 16–6	Diagnostic Accuracy of 64-Slice Computed Tomography Coronary Angiography in Patients with NSTEMI Acute Coronary Syndrome			
Analysis	**Sensitivity, % (95% CI)**	**Specificity, % (95% CI)**	**PPV, % (95% CI)**	**NPV, % (95% CI)**
No. of patients (104)	100 (95-100)	75 (47-92)	96 (89-99)	100 (70-100)
No. of segments (1525)	92 (88-96)	91 (89-92)	60 (54-65)	99 (98-99)

NPV, negative predictive value; PPV, positive predictive value

MULTISLICE COMPUTED TOMOGRAPHY CORONARY IMAGING

MSCT coronary imaging provides information about plaque size, composition of the plaque (noncalcified or calcified), degree of lumen obstruction, and vessel wall remodeling. The development of a noninvasive imaging technique to identify a high-risk plaque (i.e., a plaque with a high likelihood to rupture, with subsequent thrombus formation, resulting in an acute coronary syndrome) would be highly desirable. Assuming that the characteristics of a culprit plaque in unstable patients (ruptured or eroded plaques) resemble that of high-risk plaque (nonruptured or eroded plaque), several groups have reported the CT characteristics of these culprit lesions in comparison to stable plaque.[27-29] As assessed by CT, culprit plaques in acute coronary syndromes demonstrate a larger plaque size with more outward remodeling, spotty calcifications, and more noncalcified material when compared with stable lesions (Fig. 16-4).[27,29] CT imaging is generally limited to the morphologic aspects of plaque, although a recent animal study has demonstrated that injected iodine-containing nanoparticles, which accumulate in active macrophages in atherosclerotic plaques, could be visualized by CT.[30] In current clinical practice, however, CT is unable to identify the typical characteristics of a high-risk lesion—a large lipid core covered by a thin fibrous cap, with signs of inflammation—and cannot be used for the assessment of plaque vulnerability.

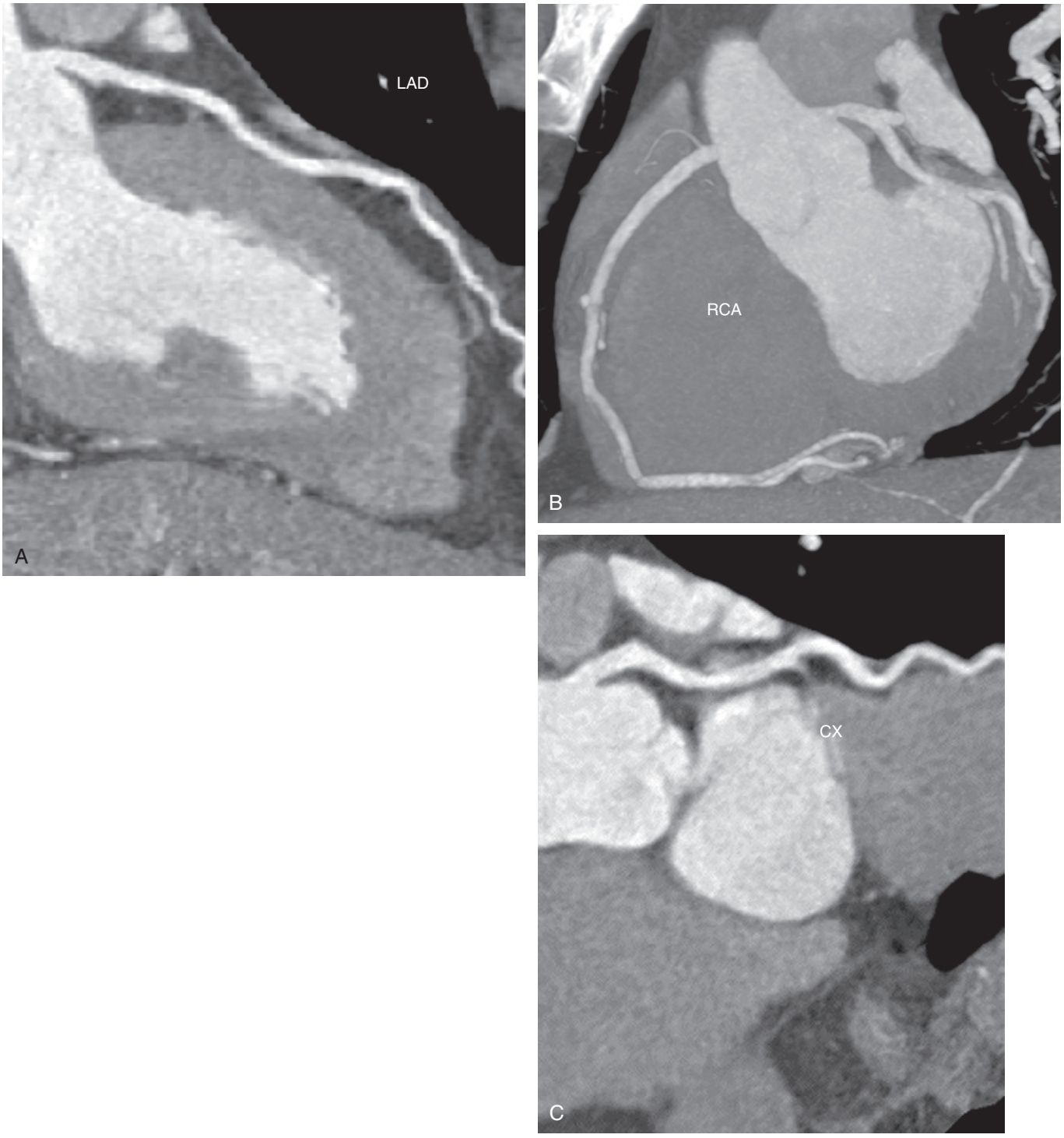

FIGURE 16–3 **A,** normal LAD; **B,** normal RCA; **C,** normal LCx. Dual-source CT coronary angiography demonstrating the absence of significant coronary stenosis of the coronary tree in a patient with acute chest pain. LAD, left anterior descending artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

In Patients with Acute Chest Pain Presenting at the Emergency Department

Traditionally, patients admitted to an emergency department with acute chest pain undergo a series of tests, including 12-lead ECG at rest, serial biomarker levels (creatine Kinase, MB fraction or troponins), or SPECT scanning, to detect or rule out the presence of an acute coronary syndrome. This process is time-consuming, usually involves hospital admission, and is costly. Noninvasive imaging with MSCT is a rapid, patient-friendly technique that may improve and accelerate diagnostic protocols for acute chest pain patients, with a reduction of costs.

Before the introduction of MSCT, the merits of EBCT calcium screening were evaluated in low-risk patients presenting at the emergency room with acute chest pain and nonspecific or normal ECG findings, normal biomarkers, and no history of coronary artery disease. McLaughlin and coworkers[31] have studied 134 patients (53 ± 2 years of age; 63% women) and recorded the occurrence of sudden death

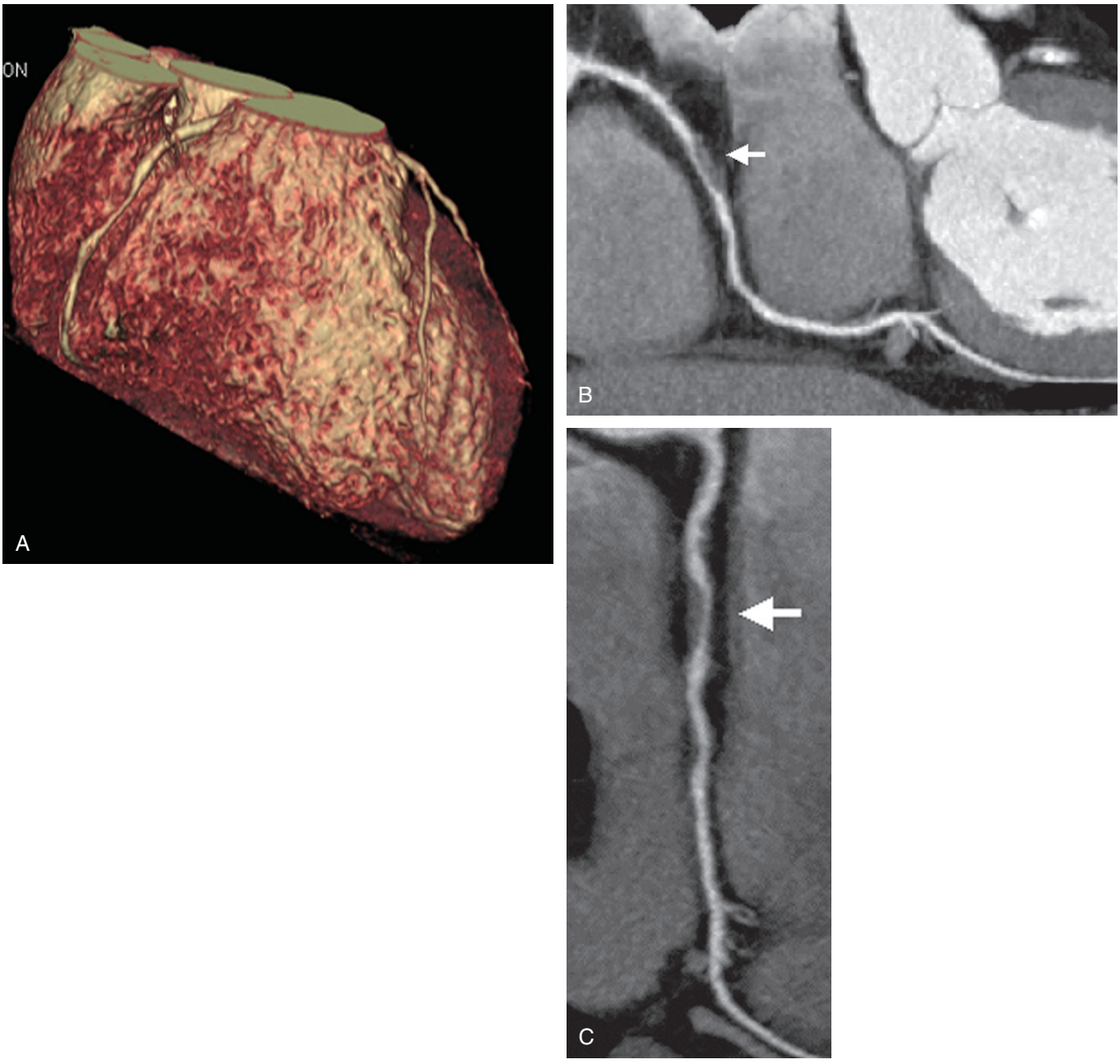

FIGURE 16–4 **A,** volume rendered image RCA; **B, C,** curved multiplanar reconstructions of RCA with severe non-calcific palque. Dual-source CT coronary angiography demonstrating a noncalcified severe lesion with outward remodeling (**B, C,** *arrows*) of the RCA. RCA, right coronary artery.

or nonfatal myocardial infarction at 30 days. No events occurred in 48 patients with a negative scan. Nonfatal myocardial infarction occurred in 4 of 86 patients with a calcium score of at least 1 (Table 16-7).

Georgiou and colleagues[32] have conducted a prospective observational study of 192 patients, (mean age, 53 ± 9 years; 46% women; follow-up duration, 50 ± 10 months). Cardiac death occurred in 11 patients and nonfatal myocardial infarction in 19 patients. Patients with a negative CT calcium scan (76) were event-free; the event rate was 26% in those with a positive CT calcium scan (116; see Table 16-7). A multivariate analysis revealed that age- and gender-adjusted calcium score risk profiles were stronger independent predictors than traditional risk factors.

Both studies were performed in relatively young patients with a low prevalence of calcium. Older patients were

TABLE 16–7 Calcium Scan as Predictive of Cardiac Death or Nonfatal Myocardial Infarction*

	Study (Year)	
Calcium Scan Follow-up	McLaughlin et al† (1999)[31] Event Rate (%)	Georgiou et al‡ (2001)[32] Event Rate (%)
No calcium	48 patients (0%)	76 patients (0%)
Calcium present	86 patients (4.4%)	116 patients (26%)

*In low-risk patients with acute chest pain presenting at the emergency department.
†Length of study: 30 days (*N* = 134).
‡Length of study: 50 ± 10 months (*N* = 192).

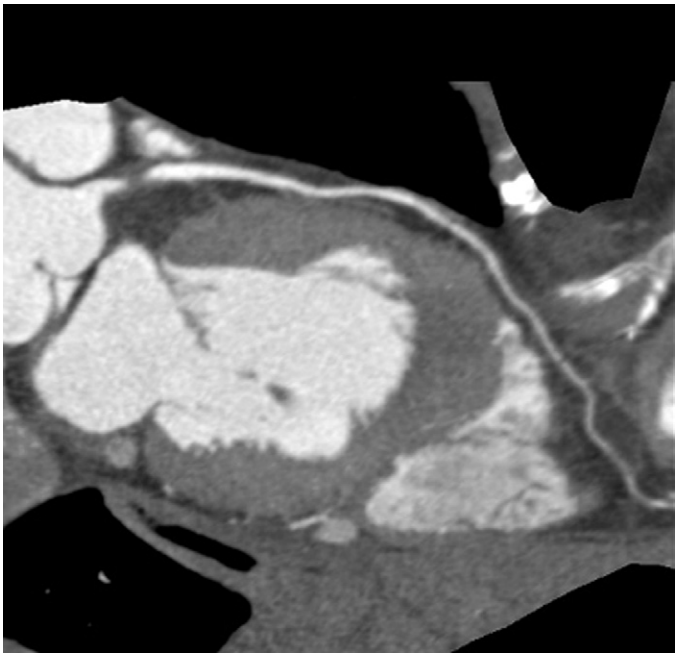

FIGURE 16–5 64-Slice CT coronary angiogram showing a significant stenosis in the proximal segment of the left anterior descending coronary artery.

excluded because the expected high prevalence of calcium would lead to a low specificity of the calcium scan, rendering this less useful in clinical practice.

Thus, low-risk patients admitted to an emergency department who have a negative CT calcium scan can be discharged safely, obviating the need for further stress testing. However, patients with a positive CT calcium scan require further investigation.

Noninvasive 64-slice coronary CT angiography accurately detects significant coronary obstructions with sensitivities and specificities between 90% and 98% (Fig. 16-5).[33] A negative CT angiogram reliably excludes the presence of significant coronary artery disease; this feature may be useful in the emergency department to discharge patients with acute chest pain quickly who have no CT evidence of atherosclerosis. Hoffmann and associates[34] have conducted a blinded prospective study in patients with acute chest pain with no ischemic electrocardiographic changes and negative initial biomarkers to evaluate the diagnostic value of 64-slice CT coronary angiography to rule out ACS. They studied 103 low-risk patients, of whom 14 were diagnosed as having an acute coronary syndrome over a 5-month follow-up. Of these, 73 patients showed no significant coronary obstruction, including 41 without any plaque by CT, none of whom had an acute coronary event. Thirteen patients had at least one significant stenosis, 8 of whom had an ACS, and 17 patients had noninterpretable scans, of whom 6 had an ACS. Comparing patients with obstructive disease or nonconclusive images with patients without significant disease, the positive and negative predictive values of CT angiography were 47% and 100%, respectively.

Rubinshtein and coworkers[35] have prospectively studied 58 low-risk patients with acute chest pain. The MSCT scan was normal in 15 patients and showed nonobstructive plaques in another 20. During a follow-up period of 15 months, no death or MI occurred in these 35 patients, and only one late PCI was necessary (2.8%). CT scans showed that 23 patients had obstructive disease (>50% diameter stenosis), of which 20 were found to have an ACS based on enzyme level increases, SPECT, or invasive coronary angiography. The sensitivity was 100% (20 of 20) and the specificity was 92% (35 of 38) to detect or exclude acute coronary syndrome, with a positive predictive value 87% (20 of 23) and negative predictive value of 100% (35 of 35).

Both prospective studies demonstrated that MSCT coronary angiography is useful in the triage of patients with acute chest pain with low-risk features (nondiagnostic ECG, initial normal enzyme levels or biomarkers). A normal CT scan indicates that these patients can be safely discharged, but the presence of obstructive CT plaque justifies further evaluation.

Goldstein and colleagues[36] have carried out a randomized study to evaluate the safety and diagnostic efficacy of 64-slice CT coronary angiography in low-risk patients presenting with acute chest pain at an emergency department with nondiagnostic ECGs and initially normal cardiac enzyme levels. After randomization, 99 patients initially underwent MSCT and 98 patients followed a standard of care diagnostic algorithm, consisting of serial electrocardiograms, cardiac enzyme levels, and SPECT rest and/or stress imaging, to rule out myocardial infarction. Study outcomes were safety (freedom from major events over 6 months), diagnostic efficacy (clinically correct and definitive diagnosis), time, and expense.

Both approaches were completely safe. MSCT excluded (n = 67) or identified (n = 8) coronary artery disease in 75% of patients (Fig. 16-6); 25% (n = 24) required stress testing because of equivocal CT outcome (intermediate lesion or nonevaluable segment). In the standard of care protocol 95% of patients (n = 93) had a normal stress test and could be discharged. The diagnostic efficacy was not statistically different between the two groups. MSCT reduced the diagnostic time to 3.4 hours compared with 15 hours ($P < .001$) and lowered costs from $1872 to $1586 ($P < .001$). The trial demonstrated that MSCT was safe and cost-effective in the triage of patients with acute chest pain considered to be at low risk.

Triple Rule-Out Protocol in the Emergency Department

Approximately 7% of all presentations to an emergency department involve patients with chest pain that is caused by an acute coronary syndrome, pulmonary embolism, or aortic dissection. In most, symptoms and clinical examination will suggest one (or none) of these potentially life-threatening conditions, which should then be followed by the appropriate diagnostic investigations and treatment. Occasionally, the clinical picture may be equivocal, in which case MSCT could be used to rule out all three urgent causes of acute chest pain, the so-called triple rule-out of an acute coronary syndrome, pulmonary embolism, or aortic dissection.

Johnson and associates[37] have investigated 55 patients with acute chest pain using the triple rule-out protocol. The CT investigations were successful in all cases. The mean craniocaudal scan range was 25 ± 4 cm and the scan duration was 22 ± 3 seconds. In 37 patients, the cause of chest pain was identified and, in the remaining 18 patients, no abnormalities were found. A coronary stenosis was detected in 9 patients (confirmed by invasive coronary angiography), a pulmonary embolism in 10 patients, and aortic dissection in 1 patient; in 7 patients a variety of abnormalities were noted that could explain the cause of pain. The study demonstrated that a triple rule-out protocol may be helpful for selected patients with unclear signs and symptoms obscuring the cause of acute chest pain.

However, the triple rule-out protocol is a nonideal compromise to image all three vascular beds. It provides lower image quality at the expense of more contrast medium and radiation exposure in comparison to dedicated scan protocols of each of the respective CT examinations to rule out aortic dissection, pulmonary embolism, or coronary artery disease.

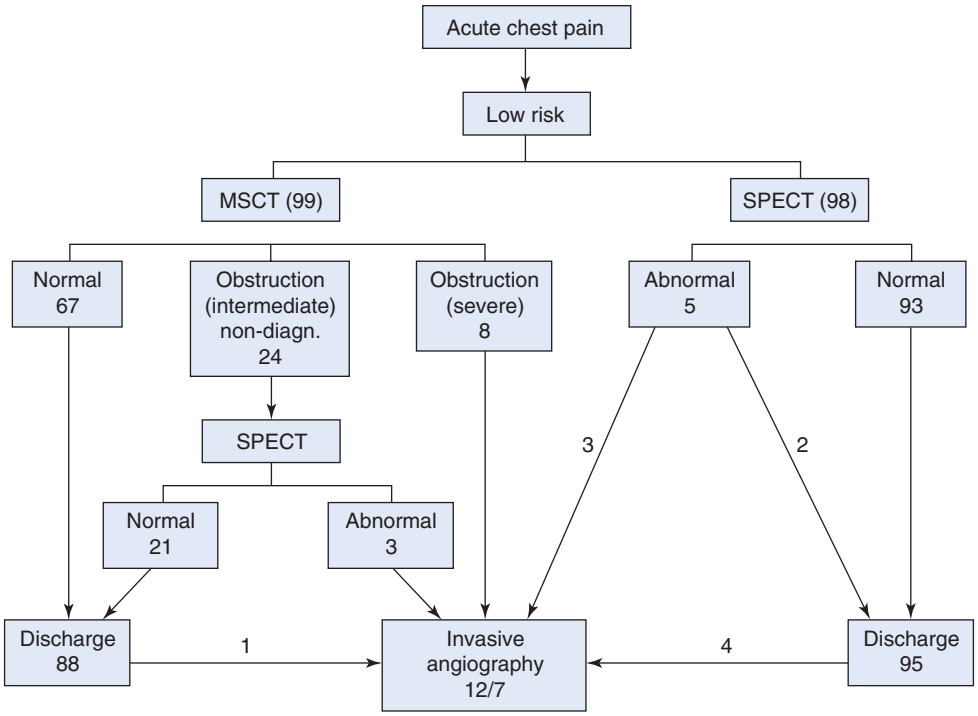

FIGURE 16–6 Flow chart of patients with acute chest pain (low risk) randomized to undergo initial MSCT or standard of care workup. *(Adapted from Goldstein JA, Gallagher MJ, O'Neill WW, et al: A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol 2007;49:650-657.)*

In most cases of acute chest pain, clinical signs and symptoms suggest a likely cause, so dedicated CT protocols should be carried out to confirm or refute clinical suspicion. This approach would ensure optimal diagnostic accuracy for each condition, in particular to confirm the presence of significant coronary artery disease, which is the most usual cause of chest pain.

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CHAPTER 17

Emerging Diagnostic Procedures for the Vulnerable Plaque

Richard Gallo and Nicolo Piazza

Coronary atherosclerotic disease is the leading cause of morbidity and mortality in the Western world.[1] Atherosclerosis is a multifocal process generally confined to the intima of the coronary arteries. Despite advances in cardiovascular imaging, current diagnostic methods have been incapable of identifying coronary events prior to their occurrence. The goal of this chapter is to review the emerging invasive imaging technologies for the detection and characterization of high-risk atherosclerotic lesions prone to rupture and cause acute coronary syndromes. Although these newer technologies are in various stages of development, some with very limited human experience, preliminary results show promise and warrant our attention.

Prior to beginning a discussion of imaging modalities suitable for the assessment of the vulnerable plaque, some key questions need to be asked:

1. What is a vulnerable plaque?
2. What are the components of the vulnerable plaque that will be useful as targets for imaging?
3. What is the gold standard for identifying the vulnerable plaque?
4. Where are vulnerable plaques located in the coronary arterial tree?
5. How many vulnerable plaques can be present in a patient at one time?
6. What is the natural history of a vulnerable plaque?
7. Which patients will require screening?
8. What are the clinical implications of finding one or more vulnerable plaques?
9. What are the potential treatments, if any?

In an attempt to answer these questions, research has been extensive but many questions remain unanswered.

A culprit plaque or lesion is generally defined after a coronary event has occurred and is considered responsible for the coronary occlusion leading to the acute coronary syndrome. In contrast, an atherosclerotic plaque prone to thrombosis and susceptible to complications leading to a culprit lesion is described as a vulnerable plaque.[2]

Retrospective histopathologic studies have identified several forms of vulnerable plaques.[2-4] The most commonly occurring vulnerable plaques are thin-cap fibroatheromas (TCFAs), plaque erosion, and calcified nodules.

Rupture of a TCFA is the most common type of plaque complication and accounts for up to 65% of symptomatic thrombotic events. Characteristics of a TCFA lesion include the following: (1) a relatively large lipid core comprising more than 40% of the plaque volume; (2) a thin fibrous cap (<100 μm); (3) inflammation with infiltration of macrophage and lymphocytes at the cap shoulders; and (4) a paucity of smooth muscle cells.[5] The second most common type of vulnerable plaque, responsible for approximately one third of acute coronary syndromes, is plaque erosion. These plaques are characterized by thrombus overlying de-endothelialized segments of vessel but with otherwise intact plaque.[6-8] Five percent of thrombotic events have been ascribed to nodular calcifications protruding from the vessel wall with overlying thrombus. A less frequent type of vulnerable plaque, characterized by the overgrowth of the vasa vasorum, can lead to intraplaque hemorrhage and thrombosis.[4]

Proximal and midportions of major coronary arteries have been shown to be the most frequent sites of plaque rupture.[9] These proximal segments of coronary arteries are thought to harbor plaques with relatively larger lipid cores compared with plaques located more distally.[10] Furthermore, two thirds or more of culprit plaques responsible for symptomatic thrombotic events are non–flow-limiting (<50%).[11,12] As a corollary, the angiographic diameter stenosis has not been shown to correlate with future thrombotic events.

A number of caveats need to be considered. According to autopsy,[11,13] angiographic,[14] and intravascular ultrasound studies,[9,15,16] patients presenting with an acute coronary syndrome may have documented plaque ruptures remote from the culprit lesion. Furthermore, plaque rupture is not synonymous with a clinically symptomatic thrombotic event and almost 5% to 15% of noncardiac deaths are found to have plaque ruptures in the coronary arterial tree. Recent reports have stressed the importance of thinking beyond the single

vulnerable plaque and taking a more systemic approach (i.e., the vulnerable patient).

What is unknown at the moment is the natural history of the vulnerable plaques. Information about the evolution of vulnerable plaques is based on retrospective data obtained from histologic ex vivo and in vivo experiments.[17] Imaging modalities capable of characterizing atherosclerotic lesions may prove helpful in understanding their natural history and detecting lesions that are at high risk for future cardiac events.

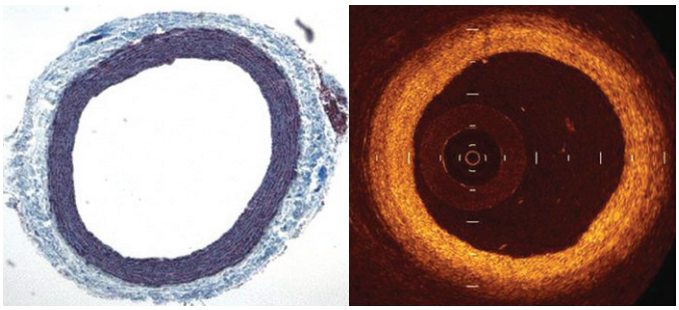
Several diagnostic imaging tools exist that are capable of evaluating determinants of plaque vulnerability. Certain high-risk features of the vulnerable plaque have been the target for vulnerable plaque imaging. Among the most common of these include the TCFA, lipid pool, and regions of high stress and inflammation. This chapter provides an overview of emerging techniques for the invasive imaging of the vulnerable plaques: (1) optical coherence tomography; (2) intravascular virtual histology; (3) intravascular palpography; (4) intravascular thermography; (5) intravascular magnetic resonance imaging; (6) Raman spectroscopy; and (7) near-infrared spectroscopy.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a light-based imaging modality resulting in near-field intensity images of tissues with high resolution. In contrast to intravascular ultrasound imaging, OCT catheters include a fiberoptic core and use a superluminescent diode to emit a scanning beam of low-coherence, near-infrared light perpendicular to the catheter axis. Back-reflection of the emitted infrared light is then captured and, using interferometry to determine the penetration depth, an image can be reconstructed.[18] Generally, to minimize energy absorption in the light beam by compounds found in blood, a center spectrum wavelength of approximately 1310 nm is used. OCT allows for in vivo real-time imaging at a resolution that is significantly higher (approximately 10 times) than that of intravascular ultrasound. The reported axial resolution of OCT is 10 to 15 μm and 20 to 25 μm for out of plane resolution. This improved resolution comes at the expense of poorer penetration through blood and tissue (1 to 3 mm).[19,20]

Cardiovascular applications have until recently been limited to in vivo experiments using postmortem aortic and coronary artery specimens.[17,18] In the last few years, OCT has become increasingly popular to follow the evolution of the newer generation of intracoronary stents.[20,21] OCT can correctly characterize individual plaque components. Decreased signal areas with poorly delineated borders is typical of a lipid-rich pool, whereas a sharply delineated region with a signal-poor interior is characteristic of a fibrocalcific plaque. A fibrous plaque is clearly identified as a homogenous signal-rich lesion (Fig. 17-1). Current OCT technology has demonstrated a sensitivity and specificity of 71% to 79% and 97% to 98% for fibrous plaques, 95% to 96% and 97% for fibrocalcific plaques, and 90% to 94% and 90% to 92% for lipid-rich plaques, respectively.[22-25]

Although OCT correlates well with many of the features found on histologic sections, a recent study by Manfrini and colleagues[26] called into question the ability of OCT to identify certain plaque features. After classifying 79 postmortem human coronary arterial sections by histology, OCT was able to identify 45% of fibrous cap atheromas correctly ($\kappa = 0.27$; $P < .01$), 68% of fibrocalcific plaques ($\kappa = 0.40$; $P < .001$), 83% of fibrous plaques ($\kappa = 0.37$; $P < .001$) and 100% of complicated lesions (all thrombi; $\kappa = 1$; $P < .001$). Because of the low OCT signal penetration, lipid pools or calcium behind thick fibrous caps were difficult to characterize.



Normal artery

FIGURE 17–1 Histologic cross section of a normal coronary artery (*left*). OCT Image of a normal coronary artery (*right*). *(Courtesy of Craig Kelly, LightLab Imaging, Westford, MA.)*

In several studies, the variance of the OCT signal has demonstrated good correlation with the density of macrophages found in the fibrous cap of plaques on histologic section and thus may serve as a surrogate marker of plaque inflammation.[27-29] OCT provides a more precise delineation of the thin fibrous cap, lipid pool, and fibrous plaque than gray-scale intravascular ultrasound.[30,31]

In vivo studies have shown OCT to provide discriminatory information on plaque morphology and composition in patients presenting with coronary artery disease. In one study, patients who presented with an acute myocardial infarction were demonstrated to have lesions associated with thinner fibrous caps versus stable angina patients undergoing percutaneous coronary intervention (PCI) (median values [interquartile range], 47.0 μm [25.3 to 184.3 μm] vs. 102.6 um [22.0 to 291.1 μm] respectively; $P = .02$).[29]

The ability of OCT to characterize atherosclerotic plaques is limited by its low depth of penetration (1 to 3 mm) and therefore full circumferential views of larger coronary arteries (>3.5 mm) may not be possible. Furthermore, signal scattering and signal attenuation caused by blood requires that blood be displaced by contrast agent flushing or low-pressure occlusive balloon inflations, resulting in a shortened time window for imaging (~2 seconds). Newer generation rapid-scan OCT systems are being developed to reduce blood-free imaging times. These newer systems use a wider range of light wavelengths (1200 to 1360 nm) and then measure the back-reflected echo time. Using Fourier transformation techniques to convert frequency domains to time domain representations, these newer systems permit image acquisitions four to five times faster. Long arterial segments being scanned during a shortened low-pressure balloon occlusion or one-bolus contrast flush without occlusion.[20]

INTRAVASCULAR ULTRASOUND–VIRTUAL HISTOLOGY

Although gray-scale intravascular ultrasound is the current gold standard to assess coronary plaques and vessel dimensions, it cannot reliably differentiate among various tissue components of the atherosclerotic plaque. Intravascular ultrasound gray-scale images are formed by processing the acoustic reflectance of tissue. However, a substantial amount of information within and between the peaks of the radiofrequency signal is unprocessed. Further analysis of this radiofrequency data from the unprocessed backscattered ultrasound signal provides an alternative to the commonly used intravascular ultrasound gray-scale image analysis. By subjecting the radiofrequency data to different mathematical algorithms,

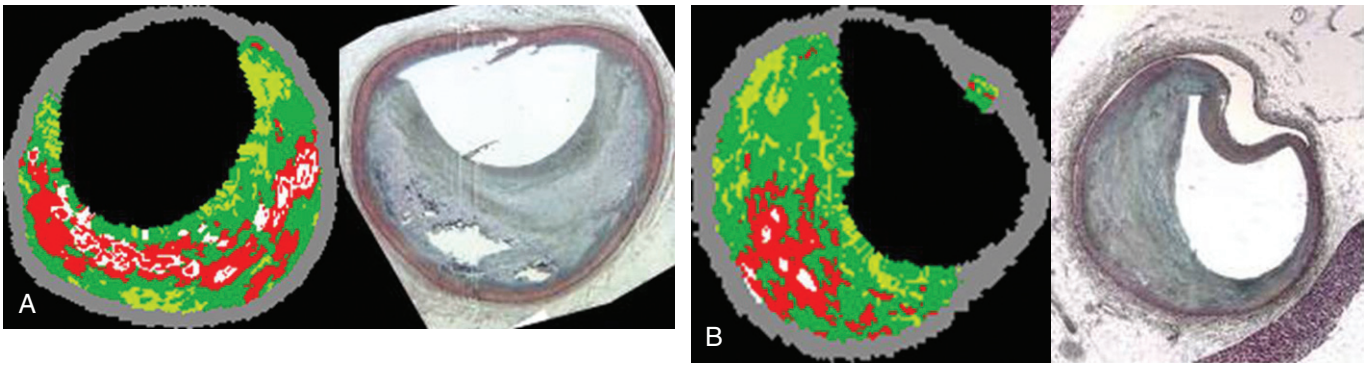


FIGURE 17–2 **A,** IVUS-VH reconstruction of a calcified fibroatheroma (*left*); histologic cross section of same calcified fibroatheroma (*right*). **B,** IVUS-VH reconstruction of a noncalcified fibroatheroma (*left*); histologic cross section of same noncalcified fibroatheroma (*right*). *(Courtesy of Michel Lussier, Volcano Corporation, Rancho Cordova, CA.)*

various geometric reconstructions revealing important histologic information can be obtained. This section will focus on intravascular ultrasound-virtual histology (IVUS-VH).[32]

IVUS-VH allows categorization of the atherosclerotic plaque into four distinct tissue components to create a colored tissue map: calcified plaque (white), fibrous plaque consisting of densely packed collagen (green), fibrolipid plaque consisting of collagen and interspersed lipid (greenish yellow), and necrotic core, including cholesterol clefts, foam cells, and microcalcifications (red; Fig. 17-2).[32]

The accuracy of IVUS-VH was evaluated in 15 patients with stable angina and in 15 patients with acute coronary syndromes using in vitro histopathology specimens obtained by directional coronary atherectomy.[33] The predictive accuracy of IVUS-VH was found to be 87.1% for fibrous, 87.1% for fibrofatty, 88.3% for necrotic core, and 96.5% for dense calcium plaques. Interestingly, IVUS-VH correctly identified a higher frequency of necrotic core in patients with non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina than in patients with stable coronary artery disease. However, directional atherectomy can disrupt the structural integrity of the tissue specimens; studies using it for comparison have therefore been criticized. In an atherosclerotic porcine model, Granada and associates[34] compared 60 lesions evaluated by in vivo IVUS-VH to sections of histology. Unlike the previous study reported, the predictive accuracy of IVUS-VH was a disappointing 38% to 58%.

Using IVUS-VH, Rodriguez-Granillo and colleagues[35] recently investigated the prevalence of TCFA and its relationship with clinical presentation. IVUS-derived TCFA was defined as a lesion fulfilling the following characteristics: (1) focal, rich necrotic core plaque (10% of circumferential surface area) in contact with the vessel lumen; and (2) atheroma volume of 40%. In this study, 23 patients with an acute coronary syndrome had a threefold higher prevalence of IVUS-derived TCFA versus 32 stable angina patients (P = .018). There was no association between patient baseline characteristics and the presence of IVUS-derived TCFA. Furthermore, 66.7% of all IVUS-derived TCFAs were clustered within the first 20 mm.

Other studies have assessed the relationship between plaque composition and vascular remodeling and clinical presentation with IVUS-VH. Areas of positive remodeling have been associated with a relatively higher content of lipid necrotic core and lower amounts of fibrous tissue.[36,37] Furthermore, coronary plaques of patients presenting with acute coronary syndrome were found to have an increased percentage of lipid core, whereas those of stable angina patients were found to have an increased fibrous content. No difference was noticed in mean calcium or fibrolipid percentage between the two groups (Fig. 17-3).[37]

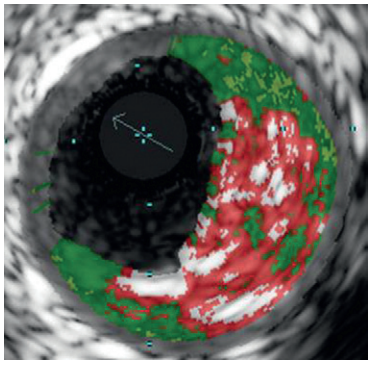


FIGURE 17–3 IVUS-VH reconstruction of a vulnerable plaque. *(Courtesy of Michel Lussier, Volcano Corporation, Rancho Cordova, CA.)*

The reproducibility of vessel geometry and plaque composition using IVUS-VH was examined in 16 nonintervened lesions during elective PCI.[38] There were small relative interobserver differences (<5%) for geometric measurements of vessel diameter and cross-sectional area. In contrast, differences were more notable for calcium cross-sectional area and necrotic core (<10%), and even more notable for fibrous (10%) and fibrolipid (24%) cross-sectional area.

The threshold value of 65 μm for defining a thin fibrous cap originated from postmortem studies.[38] Significant shrinkage of the collagen fibers of up to 80% can occur during the postmortem fixation process and, therefore, a TCFA may be larger than 65 μm. On a practical level, the axial resolution of IVUS-VH is approximately 246 μm; therefore, the absence of visible fibrous tissue overlying a necrotic core indirectly suggests a cap thickness of less than 246 μm and the absence of such tissue by IVUS-VH is used to define a thin fibrous cap.[20,36]

The current limitation of IVUS-VH is the relatively long amount of postacquisition processing required to analyze a region of interest accurately. The potential application of IVUS-VH to identify high-risk atherosclerotic lesions and predict adverse coronary events is currently undergoing clinical evaluation in an international, multicenter, industry-sponsored prospective trial (PROSPECT trial).

PALPOGRAPHY

Atherosclerotic plaques can have different mechanical stress properties, depending on their compositional tissue characteristics. Plaque rupture has been known to occur in areas with increased mechanical stress. Stress on a plaque can

increase because of the following: (1) caps become thinner; (2) lipid pools become larger; (3) difference in stiffness between the cap and lipid pool increases; and (4) inflammation weakens the cap.[39,40] In vivo, stress is imparted on the vessel lumen by the pulsatile action of intravascular blood pressure, which strains the vessel wall.[39] At a given pressure difference, soft tissues (e.g., lipids) will deform more than hard tissues (e.g., calcium).[41,42] The rate of deformation (i.e., strain) of the tissue is directly related to the mechanical properties of the tissue being investigated. Palpography assesses the first 450-μm layer of the plaque and allows for the measurement of radial stress by obtaining one strain value per angle at the lumen vessel. Because palpography only requires ultrasound data sets that are acquired at different levels of intraluminal pressure, it can be realized using conventional, clinically used catheters. IVUS palpography images are constructed using the relative local displacement between IVUS images obtained during two different intravascular blood pressure recordings and plotted as a color-coded contour at the lumen vessel boundary.[43] Regions of low strain are labeled blue and regions of high strain are labeled red to yellow.[44] A complementary image is obtained by combining the color-coded strain information and the IVUS image. With reference to IVUS palpography, a vulnerable plaque is defined as a plaque with a high strain region present at the lumen boundary surrounded by low strain values.[45]

The Rotterdam classification (ROC) score uses a 1 to 4 grading scheme to categorize plaque strain values based on the degree of tissue in proportion to the applied pressure: ROC I, 0% to <0.6%; ROC II, 0.6 to <0.9%; ROC III, 0.9 to <1.2%; and ROC IV, 1.2%.[46] A high strain spot is defined by strain values more than 1.2% (at 4-mm Hg pressure difference) that spans an arc of at least 12 degrees at the plaque surface adjacent to an area of low strain less than 0.5% (at 4-mm Hg pressure difference).[46,47]

As opposed to gray-scale IVUS images, IVUS palpography can potentially differentiate between fibrous, fibrofatty, and fatty components of plaques based on inherent differences in strain values.[47] Animal studies using Yucatan pig models have demonstrated fatty plaques to be associated with higher mean strain values and high strain spots to correlate with macrophage concentration.[48] Using postmortem histologic sections of coronary arteries, IVUS palpography was determined to have a sensitivity and specificity of 88% and 89%, respectively, for the identification of a vulnerable plaque. Furthermore, there was a correlation between higher strain levels and the amount of macrophages in the cap.[47] Reconstructed three-dimensional palpograms from 55 coronary artery disease patients revealed that patients with stable angina had fewer deformable plaques per vessel (0.6 ± 0.6) than unstable angina (1.6 ± 0.7) or acute myocardial infarction (2.0 ± 0.7) patients. Furthermore, there was a positive correlation between C-reactive protein (CRP) levels and the number of deformable plaques ($r^2 = 0.65$; $P < .001$).[49]

THERMOGRAPHY

The rich cellular environment of atherosclerotic plaques contributes to the generation of heat. Cells of the immune system produce endogenous pyrogens known as cytokines. These structurally diverse proteins are mediators of inflammation, angiogenesis, and numerous internal cellular processes. In addition to contributing to the generation of heat, cytokines mediate the acute-phase response by increased production of CRP, serum amyloid A, fibrinogen, complement proteins B, C3, and C4, interleukin-6, and a variety of proteinase inhibitors. Some of them, like tumor necrosis factor-α (TNF-α) and interleukin-1a, are able to increase endothelial cell adhesiveness and associated procoagulant effects.[50,51]

Macrophages and, to a lesser extent, T and B lymphocytes are the main cytokine producers in atherosclerotic plaques. Macrophages are abundant in atherosclerotic plaques within the plaque, often observed in the shoulder region where the fibrous cap meets normal intima.[52,53] Dense cellular regions in specimens of carotid plaques showed significantly higher temperatures when compared with the neighboring fatty core, which is often densely populated by lipid-laden macrophages.[54]

Another contributor to local heat production is plaque angiogenesis. Mediated by cytokines such as vascular endothelial growth factor, new capillaries that penetrate into the atherosclerotic plaque contribute to the elevation in the temperature profile.

There is a correlation between plaque angiogenesis and inflammation[55]; in addition, both are thought to be risk factors for plaque rupture. The release of matrix-digesting enzymes such as metalloproteinases secreted by macrophages soften the fibrous cap, enhancing the vulnerability of atherosclerotic plaques to rupture.[56]

Because inflamed plaques are at high risk for rupture with subsequent thrombosis, the development of a catheter-based or noninvasive imaging technique able to detect and distinguish vulnerable plaques could be a valuable tool for assessing prognosis and developing treatment strategies. Oscillations in the temperature of an inflamed or heat-vulnerable plaque have led to a new technique that attempts to detect local temperature fluctuations of different plaques.

It is now clear that before a plaque rupture, vulnerable plaques experience active inflammation and progressive matrix degeneration. Despite improvements in coronary imaging and identification of inflammatory markers, plaque rupture cannot be predicted by clinical means.[57] Casscells and coworkers[54] were the first to postulate that plaques covering areas infiltrated by monocytes and inflammatory cells could be identified by the heat generated and released by the activated inflammatory cells. Further studies have shown that ex vivo atherosclerotic plaques taken during carotid endarterectomy have thermal heterogeneity: Plaques with dense macrophage infiltration give off more heat than noninflamed plaques, and plaque temperature varies inversely with the thickness of the fibrous overlying cap. With the later development of a catheter-based technique to measure the temperature of human coronary arteries, thermal heterogeneity within human atherosclerotic coronary arteries was demonstrated.[58] This heterogeneity is markedly greater in patients presenting with unstable angina or acute myocardial infarction, implying that this heterogeneity may be related to the pathogenesis of these syndromes. Furthermore, the presence of higher temperatures at the site of culprit lesions in patients with unstable angina or myocardial infarction is associated with higher levels of CRP and serum amyloid A.[59]

An experimental rabbit atherosclerotic model demonstrated a direct correlation between macrophage content in atherosclerotic plaques and temperature variations. In addition, lipid-lowering therapy not only reduced macrophage plaque content, as determined by histology, but subsequently resulted in reduced temperature heterogeneity within the plaque. This suggests that thermography may be a novel method of following the macrophage burden of atherosclerotic plaques.[60]

One of the few prospective studies to correlate plaque temperature and clinical outcomes involved 86 patients with stable coronary artery disease, unstable angina, and recent acute myocardial infarction (Fig. 17-4).[61] The difference in temperature between the atherosclerotic plaque and healthy vessel wall was a strong predictor of event-free survival 1.5 years after a PCI in patients with coronary artery disease. The mean change in temperature was greater in patients with adverse cardiac events within each subgroup, although there

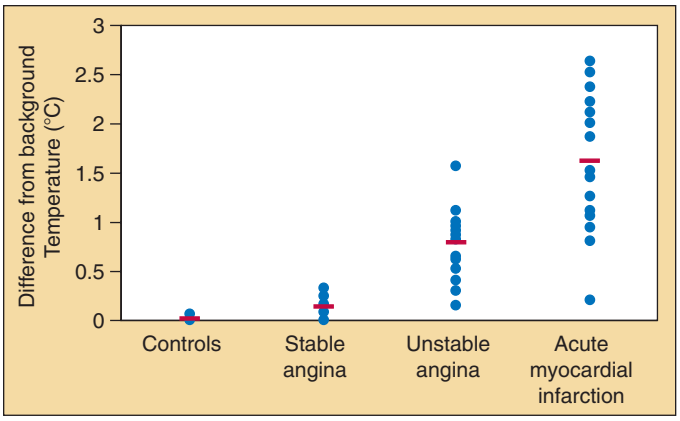


FIGURE 17–4 Progressive increase in the measured difference in maximum temperature from background temperature in patients with stable angina, unstable angina, and acute myocardial infarction. *(From Stefanadis C, Diamantopoulos I, Vlachopoulos C, et al: Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: A new method of detection by application of a special thermography catheter. Circulation 1999;99:1965-1971.)*

was a nonsignificant trend in patients with a recent acute myocardial infarction. The threshold value of temperature variation above which the rate of adverse cardiac events was significantly increased was 0.5%. Most of the cardiac events were related to restenosis of the treated lesion and not to a recurrent acute coronary syndrome.

Thermography has permitted some interesting observations on the nature of coronary plaques. In one small study involving patients with stable and unstable coronary artery disease, approximately one third of the lesions were found to be hot, indicating that plaque inflammation was fairly prevalent. In addition, the study found cold lesions in patients with unstable angina and hot lesions in patients with stable angina, suggesting that clinical presentation does not necessarily predict plaque morphology and temperature values. It was observed that patients with unstable coronary syndromes may have both hot and cold lesions only millimeters apart in contrast to findings suggesting diffuse vessel inflammation in patients with unstable coronary syndromes.[62]

The potential confounding effects of variations in coronary blood flow on measurements of plaque temperature have been examined.[62,63] This "cooling effect" of coronary blood flow is thought possibly to underestimate the true temperature of the atherosclerotic plaque. Some have suggested that correct interpretation of intravascular thermography data requires additional complementary information, such as coronary blood flow and structural characteristics of the atherosclerotic plaques.[61] A more recent prototype catheter enables temperature assessment during complete occlusion of the coronary blood flow and full apposition of the sensing elements.[62]

Current limitations to the use of thermography in clinical practice include the following: (1) cutoffs must be determined for defining vulnerability; (2) accurate temperature assessment requires direct contact of the thermistors with the vessel wall and the potential, therefore, of endothelial damage; and (3) temperature changes can occur with coronary injections of fluids or contrast and thus are to be avoided before and during the measurements.

At present, strong pathophysiologic data support the role of heat production by vulnerable plaques. The technology to measure the heat within the coronary plaques precisely is available. However promising this technology is, larger clinical trials are required to determine the sensitivity and specificity before it becomes widely available.

INTRAVASCULAR MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging is a nonionizing imaging modality that applies a surface magnetic field to biologic tissues. This results in a net alignment of the proton spins within the body parallel to the direction of the magnetic field. As short radiofrequency energy is applied, the protons absorb energy, and subsequently release it as the excited protons conform to their original state. These signals are detected by the receiver coils and subsequently interpreted.

Three imaging contrasts are used to determine plaque composition: (1) T1-weighted imaging; (2) T2-weighted imaging; and (3) proton density–weighted imaging. Information obtained about the rate of energy release (spin-lattice relaxation time) and the rate at which the spins diphase (spin-spin relaxation time) are referred to as T1- and T2-weighted measurements, respectively. Furthermore, proton density–weighted imaging can be obtained by adjusting the imaging parameters to reduce T1 and T2 contributions, leaving only the differences in water or lipid proton density.

The use of in vitro conventional magnetic resonance imaging techniques has been evaluated for the study of atherosclerotic plaques in human carotid arteries,[64,65] aorta,[66] peripheral arteries,[67] and coronary arteries.[68] The carotid arteries, because of their relatively superficial location and immobility, provide the ideal setting for in vivo imaging of the atherosclerotic vessel by conventional magnetic resonance imaging.

In contrast to conventional magnetic resonance imaging of the carotid arteries, preliminary studies in an animal pig model have quickly demonstrated the limitations of assessing the coronary arteries by conventional magnetic resonance imaging in vivo. The most important limitations included cardiac and respiratory motion artifacts and the deeply situated and relatively smaller and nonlinear course of the coronary arteries.

To overcome the potential shortcomings of conventional surface magnetic resonance imaging, placement of an intravascular receiver coil in combination with an external magnetic field is feasible.[69] The proximity of the magnetic resonance detector coil to the arterial wall would theoretically provide enhanced image quality. Intravascular coils have demonstrated good correlation between histologic sections and intravascular magnetic resonance imaging of human thoracic aortic segments. An important safety concern is vessel heating and injury caused by the energy emitted by the intravascular coil. Although the coronary blood flow may partially dissipate the heat, smaller vessels may be more prone to temperature increases.

More recently, Larose and colleagues[70] have examined the use of intravascular magnetic resonance imaging using an intravascular detector coil and external magnetic field to characterize the structure of iliac arteries of 25 human subjects and compared the results with IVUS. They found that intravascular magnetic resonance imaging visualizes the inner and outer plaque boundaries, even in the presence of extensive calcification, a factor that precluded IVUS interpretation of the vessel wall.

Conventional magnetic resonance imaging, with or without intravascular coils, requires the application of external magnets and therefore a magnetic suite. It has made such evaluations impractical in the cardiac catheterization laboratory.

Topspin Medical (Wilmington, DE) has recently developed a self-contained intravascular magnetic resonance imaging probe to image the arterial wall without the need for the application of external magnets or coils.[71] The intravascular magnetic resonance imaging probe exploits the concept of the apparent water diffusion coefficient.[64] The

self-diffusion of water molecules in a measured volume quantified by magnetic resonance imaging is referred to as the apparent diffusion coefficient (ADC) value. Previous studies using conventional magnetic resonance imaging have demonstrated that lipid-rich tissue has a significantly lower ADC value compared with that of fibrous tissue. However, the intravascular magnetic resonance imaging probe is not able to detect calcification deposits because of the relatively low concentration of hydrogen atoms available for excitation. In addition, the intravascular magnetic resonance imaging probe cannot differentiate between the fibrous cap and normal medial layer because both tissues have similar biophysical properties and, therefore, similar ADC coefficients.

The intravascular magnetic resonance imaging probe contains a strong static magnetic field gradient (~300 T/m), which makes it more than suitable for diffusion-weighted imaging to measure ADC. The depth of penetration of the field of view is roughly 50 to 200 μm into the vessel wall. It is important to realize that the intravascular magnetic resonance imaging probe does not generate an actual morphologic reconstruction of the vessel wall, but displays a color-coded map indicating the lipid composition in the field of view of probe. The system is comprised of a console similar to an IVUS console, a catheter interface unit, and the catheter. The system can be used in a conventional cardiac catheterization laboratory. Current design technology uses a self-contained 5.2-Fr intravascular magnetic resonance imaging catheter and a conventional 300-cm angioplasty wire to advance the intravascular magnetic resonance imaging probe to a maximum distance of 5 cm from the orifice of the vessel.[71]

The Topspin Medical intravascular magnetic resonance imaging probe was examined ex vivo using human aortic and coronary samples and then correlated to histologic and immunohistochemical analyses of the tissues. The probe correctly correlated with the histologic diagnosis in 15 of 16 (94%) aortic lesions and in 16 of 18 (88%) coronary lesions.

A first-in-man safety and feasibility study using the Topspin Medical probe has been completed in 29 patients. No major adverse cardiac events or device-related complications were observed. Lesions were classified as fibrous in 4, intermediate in 4, and lipid rich in 8. Six patients were excluded from analysis because of poor-quality images due to artifacts.[72]

Further studies will be needed to validate the system for clinical use. Molecular imaging of atherosclerosis coupled with magnetic resonance imaging may provide alternative and more promising modalities for imaging the vulnerable plaque.[73]

SPECTROSCOPY

Spectroscopy is the absorption, emission, or scattering of electromagnetic radiation by atoms or molecules to study the atoms or molecules qualitatively or quantitatively or to study physical processes. Spectroscopy is based on the principle that different chemical compounds absorb and scatter different amounts of energy at different wavelengths, leaving a unique chemical fingerprint.[74] Common medical applications use light or photonic energy as the radiation source. Currently, two forms of photonic spectroscopy show potential for the clinical detection of atherosclerotic and particularly vulnerable plaques, Raman spectroscopy and near-infrared diffuse reflectance spectroscopy.

Raman Spectroscopy

Raman spectroscopy is a universal analytic technique for identification of molecules in gases, liquids, and solids by the scattering of laser light. The Raman effect arises when incident light excites molecules in a sample, which subsequently scatters the light. Although most of this scattered light is at the same wavelength as the incident light, some is scattered at different wavelengths. Light that is scattered because of vibrations in molecules or optical photons in solids is called Raman scattering; it results from the molecule changing its molecular motions. The energy difference between the incident light (E_i) and the Raman scattered light (E_s) is equal to the energy involved in changing the molecule's vibrational state (i.e., getting the molecule to vibrate, E_v). This energy difference is called the Raman shift, defined by the following formula:

$$E_v = E_i - E_s$$

A plot of the incident light intensity versus Raman shift is a Raman spectrum. Different Raman spectrums are often observed, each associated with the different vibrational or rotational motions of molecules in a sample. When Raman spectroscopy is applied to an atherosclerotic plaque, the resultant spectrums can be considered to be a molecular fingerprint of that plaque.[75] This makes Raman spectroscopy potentially ideal for identifying the chemical makeup of different atherosclerotic plaques.[76]

Raman spectroscopy has been extensively validated in the ex vivo assessment of atherosclerotic plaque composition (Fig. 17-5).[77,78] Brennan and associates[79] have performed in situ chemical analysis of human coronary artery segments and successfully quantitated the levels of cholesterol, cholesterol esters, triglycerides, phospholipids, and calcium salts within the coronary plaques. The same group of investigators demonstrated the findings from Raman spectroscopy to correlate with ex vivo histologic specimens of atherosclerotic plaques obtained from human coronary and peripheral arteries.[75,80] Another ex vivo study assessed the combined approach of gray-scale IVUS and Raman spectroscopy to evaluate the atherosclerotic plaque composition of human coronary arteries; Raman spectroscopy was superior to gray-scale IVUS for the detection of the lipid core and calcium deposits.[81]

More recently, Raman spectroscopy has been challenged to assess the time-dependent plaque-stabilizing effects and chemical changes within atherosclerotic plaques induced by diet and lipid-lowering therapy. In animal studies using apolipoprotein APOE*3 Leiden transgenic mice, Raman spectroscopy showed a good correlation between total serum cholesterol exposure and cholesterol accumulation. Furthermore, Raman spectroscopy detected reductions in cholesterol accumulation associated with treatment with atorvastatin.[82,83]

These studies have provided the necessary foundation to propose Raman spectroscopy as a future catheter-based tool for the evaluation of atherosclerotic plaque composition of human coronary arteries. A Raman spectroscopy catheter designed for the in vivo assessment of human coronary arteries has been developed but has not yet been tested in human subjects. The catheter has an outer diameter of 2 mm and consists of a side view–type micro-Raman spectroscopy probe, imaging fiber bundle, and balloon. Inflation of the balloon brings the probe closer to the lumen boundary for proper evaluation.[84]

Penetration depth is limited to 1 to 1.5 mm, depending on the light source used. This limits image acquisition to the fibrous cap and within the atheromatous core. To date, experiments have been limited to direct contact with tissue; full noncontact circumferential imaging has not been evaluated. In addition, strong background fluorescence and the blood's absorbance of emitted light are technical challenges. Raman spectroscopy does not in itself provide spatial orientation or plaque geometry, and it remains to be determined whether vulnerable plaques can be differentiated from more stable sclerotic plaques solely by chemical composition. Therefore,

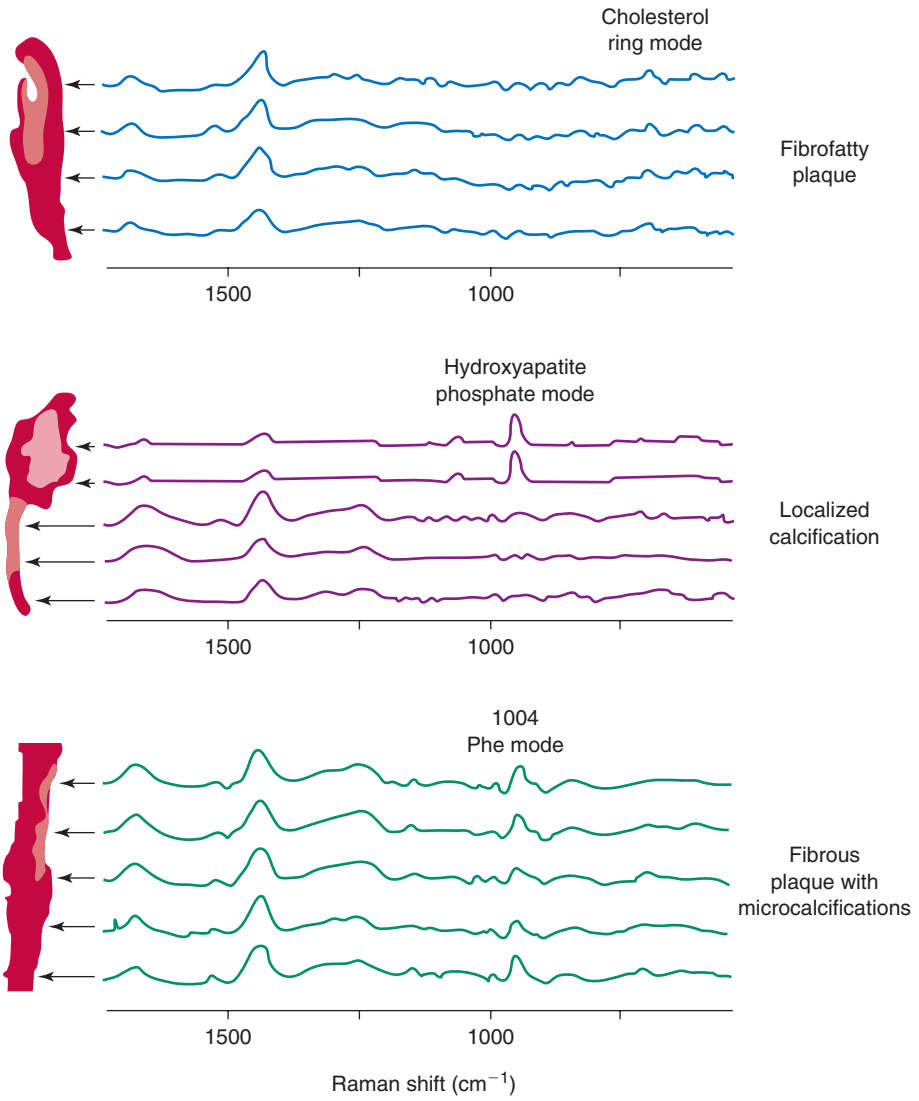


FIGURE 17–5 Cross sections from three typical human atherosclerotic arterial lesions and their corresponding Raman spectra. Each individual plaque type reveals a unique spectrum, or fingerprint. *Top,* Fibroatheromatous plaque with a lipid-rich core. *Center,* Heavily calcified plaque. *Bottom,* Fibrous plaque with scattered microcalcifications. *(From Salenius J, Brennan J, Miller A, et al: Biochemical composition of human peripheral arteries examined with near-infared Raman spectroscopy. J Vasc Surg 1998;27:710-719.)*

the future development of Raman spectroscopy as a catheter-based technology may involve a combination with another imaging modality, such as IVUS or OCT.

Near-Infrared Diffuse Reflectance Spectroscopy

Similar to Raman spectroscopy, near-infrared diffuse reflectance spectroscopy uses light to detect and determine the composition of organic substances. However, unlike Raman spectroscopy, which uses high-energy laser light in the visible light spectrum, near-infrared diffuse reflectance spectroscopy is the process of understanding how infrared light (750 to 2500 nm) interacts with various molecules (e.g., water, fat, protein, glucose). Near-infrared light occurs just beyond the location of red light in the visible spectrum.

Each type of molecule reacts and absorbs near-infrared light differently. The amount of light absorbed is proportional to the concentration of that particular molecule, revealing both qualitative and quantitative information about the pathologic process under investigation. Histologic correlation with reflectance patterns of different tissues can potentially detect and distinguish the lipid-rich atheromatous core and become a useful diagnostic tool for the detection of vulnerable plaque.

Spectroscopic systems using infrared light have demonstrated the ability to identify cholesterol, high-density lipoprotein, and low-density lipoprotein in arterial wall samples obtained at autopsy. Chemical analyses have shown that correlation of the atheromatous core content using high-pressure liquid chromatography is high.[85] In another experiment, near-infrared diffuse reflectance spectroscopy correctly identified histologic features of plaque vulnerability, including the presence of lipid-rich atherosclerotic plaques, with a high degree of sensitivity (90%) and specificity (93%) in 199 human aortic specimens taken at autopsy.[86]

Cassis and colleagues[87] were able to characterize the accumulation of low-density lipoprotein cholesterol in hypercholesterolemic rabbit aortas using near-infrared diffuse

reflectance spectroscopy. Subsequently, the lipid content of ex vivo specimens of human carotid plaques was successfully measured using near-infrared diffuse reflectance spectroscopy.[88] Furthermore, in a study of 199 human aorta specimens taken at autopsy, Moreno and associates[86] demonstrated that near-infrared diffuse reflectance spectroscopy correctly identified histologic features of plaque vulnerability with a high degree of sensitivity (90%) and specificity (93%). These same investigators found similar sensitivities and specificities for the identification of lipid-rich plaques in a study of 167 human coronary artery specimens.[89]

Despite limited experience, the technology does appear promising. A small, 3.2-Fr coronary catheter (InfraReDx, Burlington, Mass) with the ability to send and receive infrared light information has been developed. The lateral spatial resolution of the device is approximately 1 mm.[90] Unlike the case with OCT, thermography, and perhaps Raman spectroscopy, it does not appear that flowing blood interferes with the reflectance patterns of the longer wavelengths of infrared light. In a study using this device, large, lipid-rich plaques were identified (sensitivity, 88%; specificity, 79%) through up to 3 mm of blood.[91] This should permit noncontact imaging of the circumference of the vessel without the need to occlude blood flow. Although coronary artery motion may affect the acquisition of data by near-infrared diffuse reflectance spectroscopy, ultrafast systems have been developed that are capable of obtaining spectra data within 6 milliseconds by scanning only a preselected number of wavelengths appropriate for atherosclerotic plaque assessment.[92]

Although results are unpublished, clinical evaluation of a prototype near-infrared diffuse reflectance spectroscopy device was tested in patients undergoing coronary stenting. Safety was demonstrated, but substantial motion artifacts failed to prove its feasibility. Further technical advancements will address these issues and should improve on the quality of data and image acquisition.[93]

Additional studies are needed to evaluate the potential of near-infrared diffuse reflectance spectroscopy to identify plaques with high lipid content. Further refinements and developments will include the development of a nonrotating catheter, the combination of near-infrared diffuse reflectance spectroscopy with other intravascular imaging modalities such as IVUS, and the use of molecular imaging agents.

CONCLUSION

A number of intravascular imaging devices exist for the identification of the vulnerable plaque. Currently, these devices are at various stages of clinical development. Although they share the common goal of identifying the vulnerable plaque, they do so by targeting various components of the atherosclerotic plaque. These imaging modalities should be viewed as complementary; it is likely that a future definition of the vulnerable plaque may be based on a combination of criteria obtained from various imaging modalities. Future identification of a vulnerable plaque may lead to better prognostic evaluations or treatment strategies in patients with coronary artery disease.

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CHAPTER 18

Risk Stratification in Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Jessica L. Mega, Elliott M. Antman, and Marc S. Sabatine

Unstable angina (UA) is classically defined as ischemic discomfort that occurs at rest (or with minimal exertion), occurs with a crescendo pattern, or is severe and of new onset.[1] If these symptoms are accompanied by release of cardiac biomarkers of necrosis (e.g., creatine kinase MB [CK-MB] or cardiac-specific troponin) then the diagnosis of non–ST-segment elevation myocardial infarction (NSTEMI) is made.[2] Both entities typically share a common pathobiologic basis, development of a severe but nonocclusive coronary artery thrombus superimposed on a recently disrupted vulnerable plaque.[3-5] Thus, treatments for UA and NSTEMI are identical and consist of a combination of anti-ischemic and antithrombotic therapies, and potentially coronary revascularization.[6] Nonetheless, among patients presenting with UA-NSTEMI, there is substantial heterogeneity in the risk of death and major cardiac ischemic events over time. Short-term mortality is lower in patients with UA (1.7% at 30 days) as compared with those with NSTEMI or ST-segment elevation myocardial infarction (STEMI; 5.1% at 30 days for each).[7] In contrast, long-term risk of death or cardiovascular complications is higher in patients with UA or NSTEMI than in patients with STEMI. This higher risk has been associated with the increased age and burden of other diseases in patients with UA and NSTEMI.[1]

Risk stratification, aimed at providing a more accurate estimate of a patient's prognosis, is pivotal in the clinical management of patients with UA-NSTEMI.[6] Such information is important to the patient and family and also allows for more effective triage and allocation of clinical resources. Clinical trials have demonstrated the efficacy of multiple pharmacologic agents, including aspirin, adenosine diphosphate (ADP) receptor blockers, glycoprotein (GP) IIb/IIIa inhibitors, unfractionated heparin, low-molecular-weight heparin (LMWH), and direct thrombin inhibitors, as well as an early invasive strategy of management.[8-14] However, many of these treatment options are associated with bleeding, which in turn has been associated with significant morbidity and mortality.[15] Therefore, risk stratification is an integral part of clinical decision making and may guide the use of more aggressive therapy in those who are likely to derive the greatest benefit.

Data from observational studies and clinical trials have documented the prognostic usefulness of individual factors for risk stratification. Demographic and historical features, as well as information collected during the initial evaluation, including physical examination findings and electrocardiographic changes, have been used in simple risk stratification schema.[16] Elevations in various cardiac biomarkers have now been proven useful in identifying high-risk populations. The TIMI Risk Score for UA-NSTEMI and the GRACE Risk Score are two assessment tools that integrate both clinical and biomarker data. Of note, these scores and others have been designed to predict different types of events over different time periods following an acute coronary syndrome (ACS). For example, the TIMI Risk Score incorporates seven clinical predictors and evaluates the risk of mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization over the 14-day period following a UA-NSTEMI. The GRACE Risk Score, on the other hand, applies nine variables to assess the mortality risk over 6 months following STEMI, NSTEMI, or UA. Whereas both of these risk scores incorporate features on presentation, dynamic risk stratification may also provide incremental information. By integrating a combination of baseline, discharge, and follow-up data, clinicians may be able to assess a patient's risk for recurrent events more completely and accurately.

DEMOGRAPHIC AND HISTORICAL RISK FACTORS

Age

Increasing age has been shown to be a risk factor across the spectrum of ACS. For the sake of simplicity, age is often treated as a dichotomous variable (e.g., younger than 64 vs. 65 years and older). However, in an

analysis based on data from the TIMI III Registry, age was treated as a continuous variable, and each decade was found to confer a relative risk of 1.43 ($P < .001$) for the composite of death or MI over 1 year.[17] Moreover, in the PURSUIT trial, use of cubic spline functions[18,19] has revealed that the univariate relationship between age as a continuous variable and mortality was curvilinear.[20] In both UA and NSTEMI patients, an inflection point is evident at approximately 65 years, thus supporting the use of 65 years as a cut point when a binary approach is desired. An alternative approach has been to treat age as a categorical variable, with the clinician assigning increasing weight for each decade above a certain threshold.[20,21] The increase in risk with age may be steeper in patients with NSTEMI than in patients with UA.[20] Thus, clinicians should bear in mind that advanced age likely conveys increased prognostic importance when shifting from UA to NSTEMI to STEMI.[20-22]

Gender

The impact of gender on outcomes in ACS is complex. Because women with ACS tend to have more traditional risk factors, crude univariate associations showing a harmful or protective effect of female gender are likely confounded. For example, Hochman and colleagues have found that in TIMI IIIB, a clinical trial involving patients with UA-NSTEMI,[23] and in GUSTO IIb, a clinical trial that enrolled patients across the spectrum of ACS,[24] women presenting with an ACS were older and were more likely to have hypertension, diabetes, and hyperlipidemia.[25,26] Studies have revealed that women are also more likely to present with atypical features and thus may seek medical attention more slowly and may not receive appropriate care after presentation.[27,28] In angiographic studies, women presenting with presumed ACS tend to have less severe epicardial coronary artery disease (CAD) than their male counterparts.[25] To account for these gender-specific differences in ACS presentation, appropriately adjusted analyses, including age and baseline cardiovascular risk factors, are important.

In a multivariate model used to test the association of 50 baseline variables with the end point of death or MI following a non–ST-segment elevation ACS, gender was not found to be related to cardiovascular outcomes.[25] Similarly, in the development of the GRACE Risk Score (used to evaluate the mortality risk following ACS) and the TIMI Risk Score (used to evaluate the mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization risk following UA and NSTEMI), gender was not an independent predictor of poor outcomes.[29,30] Likewise, in a contemporary cohort of patients presenting with UA/NSTEMI, women and men were found to be at similar adjusted risk for subsequent cardiovascular death, myocardial infarction, or recurrent ischemia.[30a] There have been some studies in which female gender was associated with a statistically significant protective effect,[26] although this may be restricted to certain subsets of UA patients. Thus, the totality of the data suggests that female gender, after adjusting for other established predictors, conveys neither harm nor protection following a non–ST-segment elevation ACS.

Diabetes

Both in patients at risk and with known CAD, diabetes has emerged as a potent risk indicator, and is of increasing importance because of the rise in the incidence of diabetes. Over the past 2 decades, the worldwide prevalence has increased significantly, with 30 million cases in 1985 and 177 million in 2000; it is estimated that more than 260 million individuals will have diabetes by 2030.[31] In the United States, approximately 7% of the population has diabetes.[32] The metabolic syndrome is even more common, defined as the presence of at least three of the following[33]:

- Waist circumference more than 102 cm in men and more than 88 cm in women
- Serum triglyceride level of at least 150 mg/dL
- High-density lipoprotein cholesterol level of less than 40 mg/dL in men and 50 mg/dL in women
- Blood pressure of at least 130/85 mm Hg
- Serum glucose level of at least 110 mg/dL

As is the case for type 2 diabetes, insulin resistance is thought to be the underlying cause of the metabolic syndrome.[34] In the United States, the age-adjusted prevalence of the metabolic syndrome is 34% for men and 35% for women, using data from the National Health and Nutrition Examination Survey (NHANES) III.[35] The high prevalence of the metabolic syndrome also illustrates the tendency for other traditional cardiovascular risk factors to be seen in patients with glucose intolerance or overt diabetes. For example, half of diabetic patients have concomitant hypertension and one third have concomitant hyperlipidemia.

Pathophysiologically, diabetes results in increased oxidative stress[36] and the development of advanced glycation end products, which may be proatherogenic.[37] Hemostatic sequelae include heightened platelet aggregation,[38,39] increased levels of fibrinogen and plasminogen activator inhibitor (PAI) type 1,[40,41] upregulated cell surface adhesion molecules,[42,43] and impaired endothelial function.[44]

In population-based studies, it has been noted that the risk of first or recurrent MI in diabetic patients without a prior MI was approximately equal to the risk in nondiabetic patients with a prior MI.[45] In two trials of patients with STEMI—TAMI[46] and GUSTO-I[47]—patients with diabetes were found to have nearly twice the risk of death as their nondiabetic counterparts, despite similar rates of infarct-related artery patency.[48,49] In multiple clinical trials in UA-NSTEMI, including GUSTO IIb,[50] PRISM-PLUS,[11] FRISC II,[14] TACTICS-TIMI 18,[13] and GUSTO IV-ACS,[51] diabetics were found to have 1.5- to 2.0-fold higher rates of death and cardiac ischemic events. The independent prognostic significance of diabetes was demonstrated using data from the OASIS registry, which showed that diabetes was an independent risk factor for mortality in non–ST-segment elevation ACS (adjusted [adj] risk ratio [RR], 1.57; 95% confidence interval [CI], 1.38 to 1.81). Similarly, in an analysis that included 62,036 subjects across 11 TIMI trials, diabetes was independently associated with higher 30-day mortality (adj odds ratio [OR], 1.78; 95% CI, 1.24 to 2.56) and 1-year mortality (adj hazard ratio [HR], 1.65; 95% CI, 1.30 to 2.10) after UA-STEMI.[52] Moreover, the risk of death among diabetics who presented with UA-NSTEMI at 1 year approached that of nondiabetic patients who presented with STEMI, whereas the nondiabetic UA-NSTEMI patients continued on a low-risk trajectory (Fig. 18-1).

Smoking

The smoker's paradox in ACS has been described previously.[53] Current smokers tend to have lower rates of death and ischemic events than nonsmokers. This paradoxical beneficial effect appears to be explained largely by the fact that smokers present at an earlier age than nonsmokers and hence have fewer other comorbidities and less extensive CAD. Thus, among patients with ACS, although current smokers have lower event rates than nonsmokers in univariate analyses,[11,14,20] current smoking in multivariable analyses is not a significant independent prognostic factor.[20,54]

Peripheral Arterial Disease

Patients with peripheral arterial disease (PAD) frequently have significant CAD and it is not surprising that PAD is a

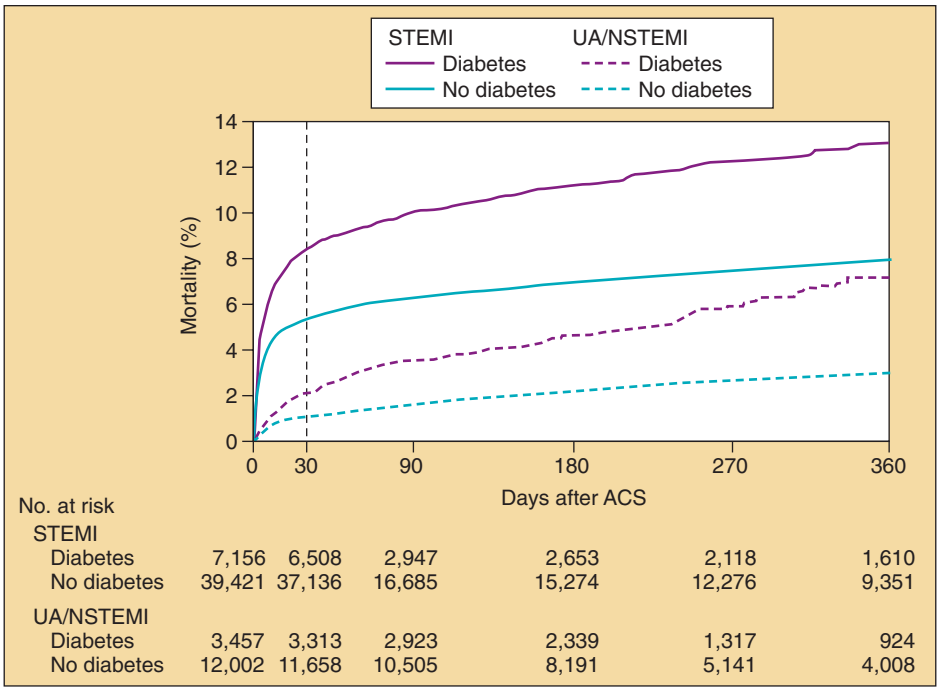

FIGURE 18–1 Cumulative incidence of all-cause mortality through 1 year after ACS. The *vertical dotted line* represents 30 days after ACS. *(From Donahoe SM, Stewart GC, McCabe CH, et al: Diabetes and mortality following acute coronary syndromes. JAMA 2007;298:765-775.)*

risk factor for death and ischemic complications in patients with UA-NSTEMI. However, in a multivariable analysis in OPUS-TIMI 16 that adjusted for other traditional risk factors, PAD remained an independent risk factor for death (adj OR, 1.44; P = .0045) as well as a composite of cardiac ischemic events (adj OR, 1.21; P = .0035); similar results were also found in the PURSUIT study.[20,55]

Prior Aspirin Use

Multiple studies have confirmed that patients with prior aspirin use are at increased risk.[30,56,57] This may be caused by the presence of aspirin-resistant platelet-rich thrombi or the greater likelihood of severe CAD in patients who present with UA-NSTEMI despite taking aspirin.[58,59] There are also some studies suggesting that patients exhibit differing degrees of aspirin responsiveness, and aspirin resistance may be associated with an increased risk of death and cardiovascular complications.[60,61]

ACUTE PRESENTATION

The tempo of the acute presentation, specific physical findings, electrocardiographic changes, and biochemical evidence of myocardial necrosis have all been shown to convey important prognostic information.

Severity of Angina

In 1989, Braunwald[16] differentiated between primary angina (caused by plaque rupture and a reduction in myocardial blood supply), secondary angina (caused by non–cardiac-induced mismatch), and postinfarction angina. He further differentiated between new-onset, crescendo, and rest angina. The importance of these distinctions has been supported in several studies, in which multiple episodes of angina in the preceding 24 hours, angina at rest, and postinfarction angina each have been shown to convey a worse prognosis.[30,62-65]

Physical Examination

Physical findings indicative of severe left ventricular contractile dysfunction, such as the presence of an S_3 gallop, rales, a mitral regurgitation murmur, hypotension, and tachycardia are more commonly seen in the setting of STEMI rather than in UA-NSTEMI, but also confer adverse prognosis in the latter syndrome. In patients with STEMI, the significance of these physical findings was noted over 40 years ago by Killip and Kimball,[66] and remain important components of contemporary integrated risk scores.[21,22] Although rarer, when they are found in UA-NSTEMI they suggest significant underlying CAD and are associated with mortality rates in excess of 60%.[67]

Electrocardiogram

The admission electrocardiogram (ECG) is one of the most useful and powerful predictors of adverse outcomes in ACS. ST-segment depression on the presenting ECG indicates severe acute ischemia and is correlated with a worse in-hospital prognosis.[7,68] The presence of ST-segment depression is also associated with greater complexity of the culprit lesion[7] and hence a greater likelihood of requiring revascularization.[17] ST-segment depression is also indicative of more extensive CAD[7,17] and is associated with worse outcomes at 6 months[7] and at 1,[17] 4,[69] and 10 years.[70]

Importantly, ST-segment deviation of as little as 0.05-mV conveys a higher rate of adverse events. In the TIMI III Registry, patients with 0.05-mV ST-segment depression had an approximately twofold higher risk of death or MI at 30 days and at 1 year.[7,17] Moreover, there appears to be a gradient of increasing risk with the increasing degree of ST depression. Among patients with non–ST-segment elevation ACS, the

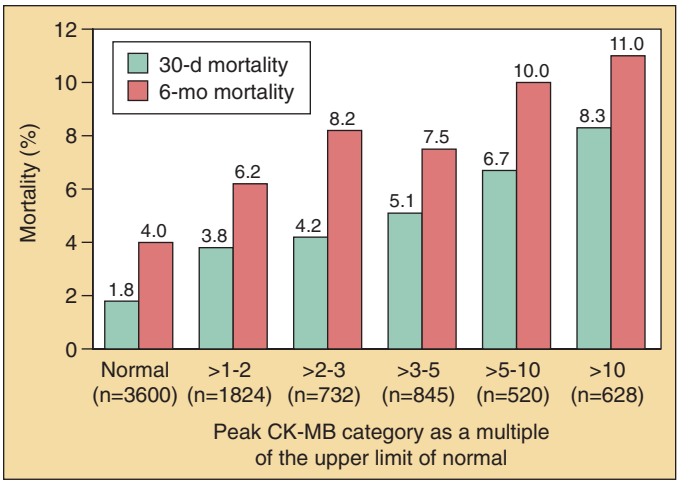

FIGURE 18–2 Mortality rates at 30 days and 6 months by peak CK-MB levels in the PURSUIT trial. *(From Alexander JH, Sparapani RA, Mahaffey KW, et al: Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. PURSUIT Steering Committee. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. JAMA 2000;283:347-353.)*

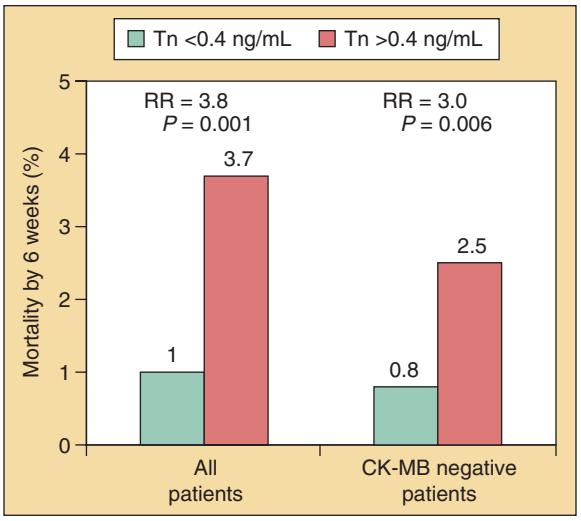

FIGURE 18–4 Mortality rate at 42 days by baseline cardiac troponin I status in the total group *(left)* and in patients with positive creatine kinase MB (CK-MB) results *(right)*. Tn, troponin. *(Data from Antman EM, Tanasijevic MJ, Thompson B, et al: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342-1349.)*

4-year survival for patients with 0.05-, 0.10-, or 0.20-mV or more ST-segment depression was 82%, 77%, and 53%, respectively ($P < .0001$).[69]

In contrast to ST-segment depressions, T-wave inversions in general have not been shown to be associated with a worse prognosis.[17] However, deep (≥0.20-mV) precordial T-wave inversions are suggestive of LAD disease and are associated with a worse prognosis.[71,72]

Detection of Necrosis

Another important predictor of outcome is the detection of myocyte necrosis. Patients with documented biochemical evidence of myocyte necrosis have higher mortality rates than patients without elevations.[73] Furthermore, there is a quantitative relationship between the magnitude of CK-MB elevation and the risk of death (Fig. 18-2).[74]

Cardiac-specific troponins, with their superior sensitivity and specificity, have emerged as the biomarkers of choice for detecting myocyte necrosis.[2] As with CK-MB, there is a clear relationship between the magnitude of troponin level elevation and mortality (Fig. 18-3).[75,76] With greater clinical sensitivity, troponins have enabled the detection of microinfarctions in approximately 30% of patients who otherwise would have been diagnosed as having UA.[75] These patients, with an elevated troponin but negative CK-MB level, have been shown to be at a three- to fourfold greater risk of dying compared with patients with negative troponin and CK-MB levels (Fig. 18-4).[75-77]

There had been debate about what the appropriate cut point(s) for troponin assays should be. Consensus panels recommended that a single cut point be adopted based on the 99th percentile in a cohort of healthy individuals and a coefficient of variation less than 10%.[78,79] However, work from

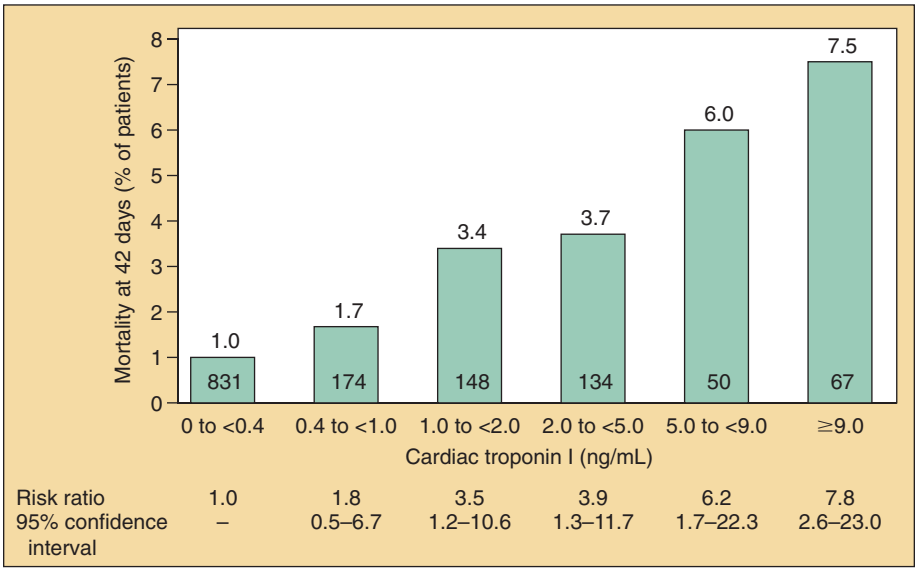

FIGURE 18–3 Mortality rate at 42 days by baseline cardiac troponin I levels in the TIMI IIIB Trial. *(From Antman EM, Tanasijevic MJ, Thompson B, et al: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342-1349.).*

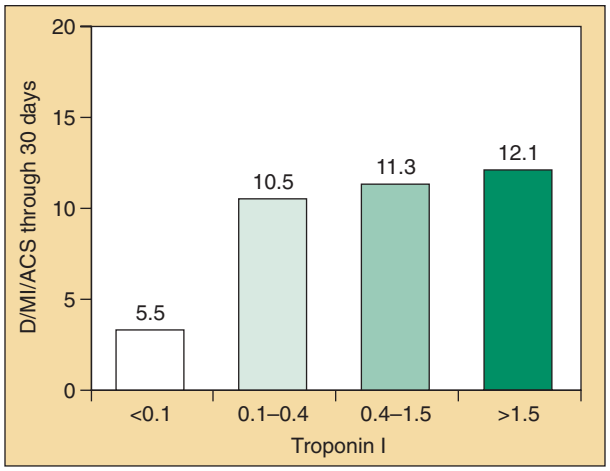

FIGURE 18–5 Death (D), myocardial infarction (MI), or rehospitalization through 30 days by baseline cardiac troponin I levels in the TACTICS-TIMI 18 trial. For the Bayer troponin I assay, the 97.5th percentile in healthy controls is 0.1 ng/mL, the level at which the assay has a 10% coefficient of variation is 0.4 ng/mL, and the level that corresponds to an MI defined by creatinine kinase MB elevation is 1.5 ng/mL. *(Data from Morrow DA, Cannon CP, Rifai N, et al: Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction. JAMA 2001;286:2405-2412.)*

trials of UA-NSTEMI has supported the prognostic importance of low-level troponin elevations, even below such cut points (Fig. 18-5).[80] Moreover, with the advent of ultrasensitive assays capable of detecting troponin at picogram per milliliter levels, troponin may be evolving from a semiquantitative variable (undetectable or a measurable level) to a true continuous variable that is detectable in all individuals. The prognostic significance in ACS of troponin levels below the 99th percentile remains to be defined.

Myoglobin is a small cytosolic protein found in myocardial and skeletal muscle and is one of the earliest markers to be released in the circulation following a MI. Although not specific for myocardial injury, myoglobin is a sensitive marker, especially in the first 4 to 8 hours after the onset of necrosis.[81-83] Heart-type fatty acid binding protein (H-FABP) is another cytosolic protein released from the cardiomyocyte in response to myocardial injury. In a study that included patients across the spectrum of ACS, elevated levels of H-FABP were significantly associated with major cardiac events independent of other established clinical risk predictors and biomarkers.[84] Whether either of these markers will be of value in the setting of ultrasensitive troponin assays remains to be determined.

INTEGRATED APPROACHES

Although the prognostic information associated with each of the variables described is useful, focusing on a single variable does not permit the clinician to use all the information at his or her disposal. For example, a patient may have negative cardiac biomarkers, but be older, with multiple cardiac risk factors, have had a prior MI, and be presenting with severe angina with ST-segment depressions, despite being on an aspirin regimen. Clearly, this patient is at high risk for death or cardiac ischemic events over the ensuing days and weeks, despite not having an elevated CK-MB or troponin level. Thus, relying on one predictor while ignoring others may lead to misclassification of a patient's risk.

The need for an integrated approach was recognized more than a decade ago with the Braunwald classification of unstable angina.[16] Although typically used to grade the severity of the acute presentation, the classification system actually contains four axes—severity of acute symptoms, clinical circumstances, intensity of medical treatment, and electrocardiographic changes. The acute presentation (Class I, II, or III) was categorized as new-onset or crescendo angina without rest pain, angina at rest, but not within the preceding 48 hours, and angina at rest within 48 hours. The clinical circumstances (A, B, or C) were divided into secondary angina caused by an extracardiac condition that intensified myocardial ischemia, primary angina presumably caused by plaque rupture, and postinfarction angina. The intensity of medical treatment (denoted with subscripts 1, 2, or 3) ranged from angina occurring in the setting of no treatment, during treatment for chronic angina, and despite maximal antiischemic therapy. Finally, patients were divided into those with and without transient ST-T–wave changes during pain. Prospective validation of the Braunwald classification system confirmed the usefulness of such an approach.[85,86]

The completion of several recent clinical trials in which a wealth of baseline clinical, electrocardiographic, and serum marker data was gathered offered the opportunity to develop modern integrated approaches to prognostication in UA-NSTEMI. Using these data, several risk scores have been developed.[20,29,30,57] One example is the TIMI Risk Score for UA-NSTEMI, which was designed to provide clinicians with a prognostic tool with high discriminatory ability using baseline variables that are part of the routine medical evaluation.[30]

TIMI Risk Score for Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Developing a Model

The TIMI Risk Score for UA-NSTEMI was developed in a derivation cohort consisting of 1957 patients who were randomized to the unfractionated heparin (UFH) arm of the TIMI 11B trial. Potential predictor variables were selected from baseline characteristics that could be readily identified at presentation and that had previously been reported to be important variables in predicting outcome (Table 18-1). Using multivariable logistic regression, seven independent, statistically significant predictors of the composite end point at 14 days were identified: age, 65 years or older; three or more risk factors for CAD; prior coronary artery stenosis 50% or higher; severe anginal symptoms (two or more anginal events in prior 24 hours); use of aspirin in last 7 days, ST-segment deviation, 0.05-mV or more; and an elevated serum cardiac marker level (CK-MB or cardiac-specific troponin). The final model demonstrated excellent calibration of the model predictions to the observed event rates (Hosmer-Lemeshow statistic,[87] 3.56_{df8}; $P = .89$) as well as good overall predictive capacity of the model (C-statistic, 0.65). Because the magnitudes of the prognostic significance (i.e., the odds ratios) for each independent predictor variable were similar, the TIMI Risk Score for UA-NSTEMI was constructed as the simple arithmetic sum of the number of predictors. Thus, the risk score is calculated by assigning 1 point for each variable that is present (Table 18-2).

Of note, the application of the C-statistic in the setting of prognostication has been debated.[88,89] The C-statistic (area under the receiver operating characteristic curve) is useful in the setting of diagnostic testing, where the sensitivity and specificity of tests are important in discriminating diseased versus nondiseased patients. However, the C-statistic may not be the ideal parameter to assess models or variables that aim to predict future risk or separate subjects into distinct risk groups.[88] For example, the C-statistic is altered minimally by accepted risk factors such as hypertension and cholesterol

TABLE 18–1 Baseline Characteristics Analyzed for Development of the TIMI Risk Score for UA/NSTEMI

	Univariate Analysis		Multivariable Analysis	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age ≥65 years	1.60 (1.25-2.04)	<.001	1.75 (1.35-2.25)	<.001
Three or more risk factors for CAD*	1.45 (1.10-1.91)	.009	1.54 (1.16-2.06)	.003
Prior coronary stenosis ≥50%	1.73 (1.34-2.23)	<.001	1.70 (1.30-2.21)	<.001
Prior MI	1.27 (0.99-1.63)	.06		
Prior CABG	1.35 (0.97-1.88)	.07		
Prior PTCA	1.62 (1.16-2.26)	.004		
ST deviation ≥0.05 mV	1.40 (1.06-1.85)	.02	1.51 (1.13-2.02)	.005
Severe anginal symptoms (≥two anginal events in prior 24 hours)	1.57 (1.24-2.00)	<.001	1.53 (1.20-1.96)	.001
Use of aspirin in last 7 days	1.86 (1.26-2.73)	.002	1.74 (1.17-2.59)	.006
Use of IV UFH within 24 hours of enrollment	1.18 (0.92-1.51)	.19		
Elevated serum cardiac markers (CK-MB or troponin)	1.42 (1.12-1.80)	.004	1.56 (1.21-1.99)	<.001
Prior history of CHF	0.90 (0.53-1.53)	.70		

*Risk factors included family history of CAD, hypertension, hypercholesterolemia, diabetes, or being a current smoker.

CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; NSTEMI, non–ST-elevation MI; OR, odds ratio; PTCA, percutaneous transluminal coronary angioplasty; UA, unstable angina; UFH, unfractionated heparin.

Adapted from Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non–ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835–842. ©2000, American Medical Association.

levels, although these variables are clearly important in classifying an individual's risk of cardiovascular disease. Thus, it has been suggested that prognostic models should be evaluated based on their calibration and ability to reclassify individuals, in addition to their ability to alter the C-statistic.[90]

Clinical Usefulness of the Model

Application of the TIMI Risk Score for UA-NSTEMI to patients in the UFH derivation cohort revealed that the score has several features desirable in risk stratification. First, there was a progressive, significant pattern of increasing event rates for the composite end point of death, MI, and urgent revascularization ($P < .001$ by χ^2 for trend; Fig. 18-6) with increasing TIMI Risk Score. Second, this pattern was also seen for each individual component of the composite end point ($P < .001$ by χ^2 for trend for each component).[30] Third, the TIMI Risk Score categorized patients into a wide range of risk. Patients with a score of 0 or 1 had less than a 5% rate of death, MI, or urgent revascularization, whereas patients with a score of 6 or 7 had more than a 40% rate of these events.

TABLE 18–2 TIMI Risk Score for UA/NSTEMI

Charactersitic	**Points**
Historical	
Age ≥65 years	1
Three or more risk factors for CAD	1
Known CAD (stenosis ≥50%)	1
Aspirin use in past 7 days	1
Presentation	
Recent (≤24 hr) severe angina	1
ST deviation ≥0.5 mm	1
↑ Cardiac markers	1
Risk Score = Total Points	(0-7)

CAD, coronary artery disease; NSTEMI, non–ST-elevation myocardial infarction; UA, unstable angina.

Validation of the Model

The TIMI Risk Score for UA-NSTEMI has subsequently been validated in many other cohorts, including ESSENCE and TACTICS-TIMI 18.[13,30] The TIMI Risk Score was designed to facilitate risk stratification in patients with UA-NSTEMI. It was not designed to aid in the diagnosis of UA-NSTEMI, which remains a clinical diagnosis that may be supported by appropriate electrocardiographic changes and, in the case of NSTEMI, requires elevated myonecrosis biomarkers. Nonetheless, the TIMI Risk Score has been applied to unselected patients presenting to an emergency department with chest pain and performed well in terms of predicting major cardiac adverse events, including death, MI, and severe ischemia requiring coronary revascularization, with the event rates

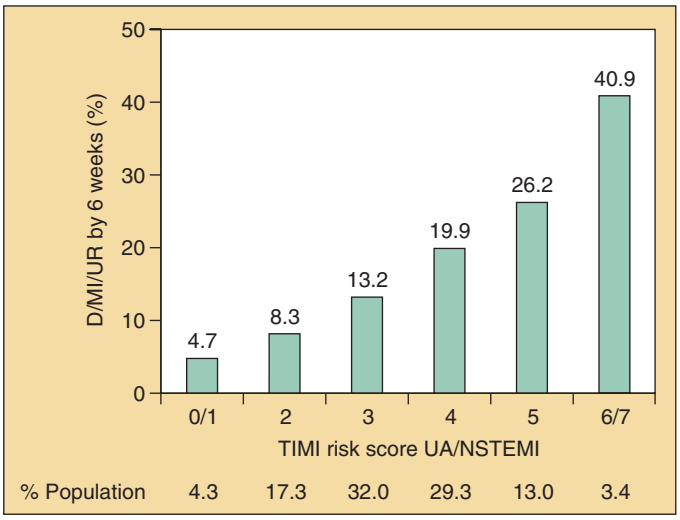

FIGURE 18–6 Death (D), myocardial infarction (MI), or need for urgent revascularization (UR) through 6 weeks by TIMI Risk Score in the unfractionated heparin arm of the TIMI IIB trial. *(Data from Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835-842.)*

ranging from 0% among patients with a score of 0 to 70% among patients with a risk score of 6 or 7 ($P < .0001$).[91]

GRACE Risk Score

Data from the Global Registry of Acute Coronary Events (GRACE) were used to create a simple decision tool for bedside estimation of 6-month mortality risk in patients who survive their ACS admission.[29] The GRACE Risk Score was developed in a cohort of 15,007 subjects and was subsequently validated in 7638 subjects across the spectrum of ACS. The final score includes nine predictive variables: older age, history of myocardial infarction, history of heart failure, increased pulse rate at presentation, lower systolic blood pressure at presentation, elevated initial serum creatinine level, elevated initial serum cardiac biomarker levels, ST-segment depression on presenting ECG, and not having a percutaneous coronary intervention performed in hospital. The C-statistics for the development and validation cohorts were 0.81 and 0.75, respectively.

Thus, integrated risk scores such as the TIMI Risk Score for UA-NSTEMI and GRACE Risk Score serve as simple bedside tools for predicting death and/or cardiac ischemic events. Clinicians can use the prognostic information from risk scores to guide their decisions regarding triage and clinical resource allocation during the patient's index hospitalization. Moreover, such risk scores appear to predict not only which patients will have acute events, but also which patients are at risk for dying or suffering cardiac ischemic events after discharge.[92]

NOVEL CARDIAC BIOMARKERS

Several new biomarkers have been utilized that provide insight into different aspects of the pathophysiology of ACS.

C-Reactive Protein

C-reactive protein (CRP) has been used for decades as a marker of systemic inflammation. It is now appreciated that inflammation plays a central role in atherosclerosis and that CRP itself may play a direct role in causing thrombosis.[93] Data from the Physician's Health Study have revealed that among healthy individuals with a normal CRP, below 1.5 mg/dL, there is a gradient of risk for MI with increasing CRP levels.[94] Studies in patients with ACS revealed that patients with an elevated CRP have worse short-term and long-term outcomes.[95,96] Even after accounting for troponin, in several studies CRP proved to be a potent predictor of short-term and long-term mortality (Fig. 18-7).[96,97] There is no specific cut point that is universally agreed on in the setting of an ACS, but the National Academy of Clinical Biochemistry (NACB) guidelines recognize 15 mg/L.[98] This cut point is the 99th percentile in healthy adults, has established prognostic usefulness in ACS,[97] and has been shown to be as good if not better than other cut points across the spectrum of ACS.[99,100]

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is synthesized and released by the ventricles in response to overload. Measuring BNP levels has proven useful in diagnosing and optimizing treatment for heart failure.[101,102] BNP levels have also been shown to be elevated in ACS.[103] De Lemos and associates[104] have demonstrated that the baseline level of BNP is correlated with the risk of death, MI, and congestive heart failure through 10 months (Fig. 18-8). This relationship held true for STEMI, NSTEMI, and UA. It may be that ischemia-triggered transient left ventricular (LV) systolic and diastolic dysfunction leads

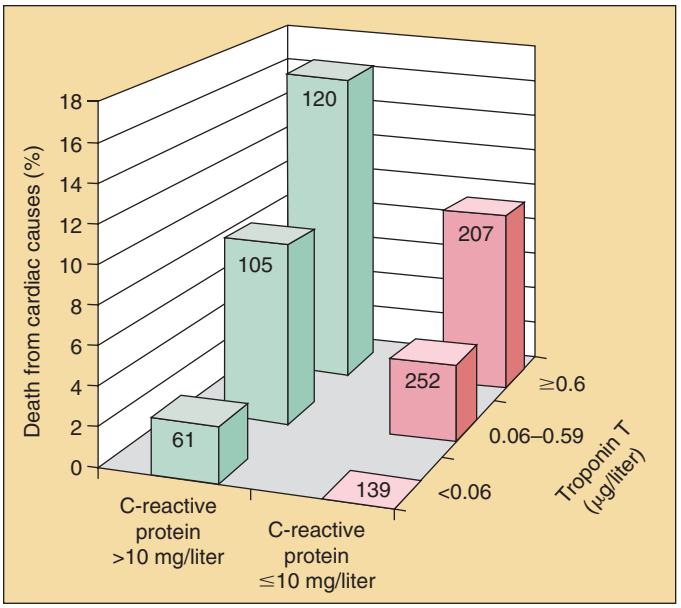

FIGURE 18–7 Cardiovascular mortality rate through 2 years by baseline C-reactive protein and cardiac troponin T levels in the FRISC trial. *(From Lindahl B, Toss H, Siegbahn A, Venge P, et al: FRagmin during Instability in Coronary Artery Disease. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med 2000;343:1139-1147.)*

to the release of BNP; thus, BNP levels may reflect not only any underlying impairment in LV function, but also the severity of the acute ischemic insult.[105]

Now that CRP and BNP assays are widely available, these biomarkers offer the opportunity to improve our ability to risk-stratify patients with UA-NSTEMI using a multimarker approach. Using data from two contemporary ACS trials (OPUS-TIMI 16[106] and TACTICS-TIMI 18[13]), patients were categorized on the basis of the number of elevated biomarkers at presentation.[107] Each additional biomarker that was elevated led to a doubling of mortality risk (Fig. 18-9). Similar relationships exist for the end points of MI, CHF, and the composite. In a multivariable analysis that adjusted for clinical factors, including age, diabetes, prior MI, and ST-segment depression, patients with one, two, and three elevated biomarkers had a 2.1-, 3.1-, and 3.7-fold increase in the risk of death, MI, or CHF through 6 months ($P < .01$ for each hazard ratio). The incorporation of these new markers into existing integrated risk scores may be a useful next step.

Myeloperoxidase

Myeloperoxidase (MPO) is a peroxidase enzyme found in neutrophil granulocytes and exhibits multiple proatherogenic effects. In patients with UA or NSTEMI, MPO concentrations predicted an increased risk for subsequent death or MI over 6 months (adj HR, 2.11; 95% CI, 1.21 to 3.67; $P = .008$), independent of other risk factors or biomarkers.[108] In a study using coronary balloon angioplasty to induce coronary plaque injury, investigators observed rapid activation of neutrophils, increased arterial levels of MPO, and impaired vascular nitric oxide bioavailability as measured by brachial flow-mediated dilation.[109] These findings suggest that MPO may play a more direct role in the progression of vascular disease and dysfunction.

Growth Differentiation Factor-15

Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor–cytokine superfamily, is secreted

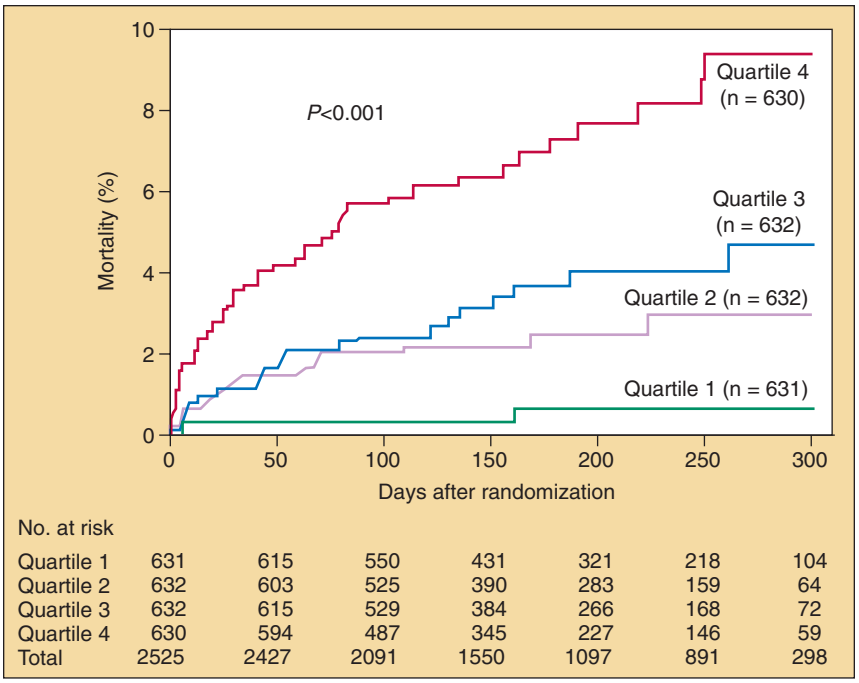

FIGURE 18–8 Mortality rate through 10 months by baseline B-type natriuretic peptide quartile in the TACTICS-TIMI 18 trial. *(From de Lemos JA, Morrow DA, Bentley JH, et al: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014-1021.)*

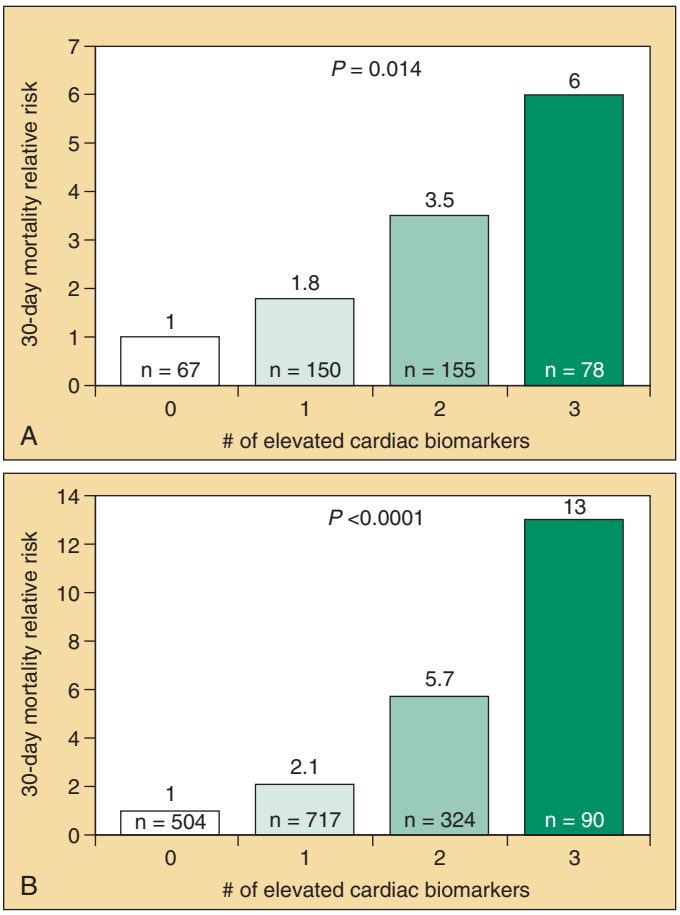

FIGURE 18–9 Relative 30-day mortality risks in patients stratified by number of elevated cardiac biomarkers (troponin I, C-reactive protein, and B-type natriuretic peptide) in OPUS-TIMI **(A)** and TACTICS-TIMI 18 **(B)**. *(From Sabatine MS, Morrow DA, de Lemos JA, et al: Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: Simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002;105:1760-1763.)*

by cardiomyocytes during ischemia and reperfusion. In GUSTO IV, increasing tertiles of GDF-15 in non–ST-segment elevation ACS patients were associated with an enhanced risk of death at 1 year (1.5%, 5.0%, and 14.1%; $P < .001$), and GDF-15 was shown to be an independent predictor of mortality following adjustment for baseline clinical features and other biomarkers.[110] In FRISC-II, the investigators tested whether circulating levels of GDF-15 could assist with identifying patients who benefit most from an invasive treatment strategy in the setting of non–ST-segment elevation ACS. They found that an invasive strategy reduced the occurrence of death or MI in patients with GDF-15 levels 1800 ng/L or higher (HR, 0.49; 95% CI, 0.33 to 0.73; $P = .001$), between 1200 and 1800 ng/L (HR, 0.68; 95% CI, 0.46 to 1.00; $P = .048$), but not less than 1200 ng/L (HR, 1.06; 95% CI, 0.68 to 0.65; $P = .81$).[111] Thus, GDF-15 appears to be an independent predictor of 1-year mortality in post-ACS populations and is a promising new biomarker that may be able to assist with therapeutic decisions.[112]

RISK STRATIFICATION AND CLINICAL DECISION MAKING

Risk stratification is not only useful for prognosis, but offers the opportunity to help guide the use of specific therapies. In particular, the use of a LMWH, the use of a GP IIb/IIIa inhibitor, and an early invasive strategy represent three treatment decisions about which clinicians continue to debate.[6] All three treatments have been shown to be beneficial in large randomized trials. Nonetheless, the cost and potential complications associated with each of these treatments suggest the need for identifying patients who would derive particular benefit from these therapies.

In addition to their powerful prognostic role, troponin levels can also be used to guide therapy. In several of the trials of GP IIb/IIIa inhibitors in UA-NSTEMI, baseline blood samples were available for the assessment of troponin levels. The message from each trial is remarkably consistent. In CAPTURE,[113] PRISM,[114] PRISM-PLUS,[115] PARAGON-B,[116] and ISAR REACT 2,[117] among patients with elevated baseline troponin levels, the addition of a GP IIb/IIIa inhibitor

was associated with 30% to 80% relative risk reductions. In contrast, among patients with normal troponin levels, there was no demonstrable benefit. Troponins have also proven useful in the setting of other potent medical therapies, such LMWHs. Patients with elevated troponin levels have been shown to derive particular benefit both from short-term and extended therapy with LMWHs.[118,119]

A similar interaction was seen between troponin status and the benefits of an early invasive strategy in the TACTICS-TIMI 18 trial. Patients with an elevated troponin level had a 39% relative risk reduction in the primary end point with the early invasive strategy versus the conservative strategy.[80] In contrast, there was no benefit with the early invasive strategy in patients with normal troponin levels. In the ICTUS trial, 1200 non–ST-segment elevation ACS subjects with an elevated cardiac troponin T level (0.03 μg/L) and either ECG evidence of ischemia at admission or a documented history of CAD were randomized to an early invasive or conservative treatment strategy. Despite the elevated troponin level status, the rates of death, nonfatal MI, or rehospitalization for angina over 1 year were similar in the two treatment arms (relative risk [RR], 1.07; 95% CI, 0.87 to 1.33; $P = .33$).[120] Of note, the ICTUS trial applied a range of CK-MB cut points in their definition of MI; however, the ICTUS investigators subsequently applied the MI definitions from FRISC-II and TACTICS-TIMI 18 and found that although these definitions lowered the rates of MI, the relative risks remained similar. When further examining MI rates, the risk of periprocedural MI was higher in those treated with an invasive strategy; however, the risk of spontaneous MI was lower in this group, consistent with what has been observed in a meta-analysis of all prior trials.[121]

Such binary categorization of troponin status—either positive or negative—may be too simplistic.[122] Although there is a steady monotonic rise in mortality risk with increasing troponin levels,[75] the risk of recurrent MI appears to have a U-shaped relationship to troponin levels.[123] Furthermore, although when viewed as a whole, troponin-positive patients benefit from GP IIb/IIIa inhibitors and an early invasive strategy, the magnitude of benefit follows a U-shaped curve in relation to the degree of troponin elevation. In PRISM, the benefit of tirofiban in reducing death or MI was nonexistent in patients with undetectable or minimal levels of troponin, greatest in patients with intermediate elevations of troponin, and more modest in patients with higher levels of troponin.[114] A similar U-shaped interaction was seen in TACTICS-TIMI 18 in regard to troponin elevations and the benefit from an early invasive strategy.[80]

Another prognostic factor that has been shown to convey therapeutic implications is diabetes. In a meta-analysis of the six major trials examining the use of GP IIb/IIIa inhibitors in UA-NSTEMI, treatment with a GP IIb/IIIa inhibitor was associated with a statistically significant 26% reduction in mortality in diabetics (Fig. 18-10).[124] In contrast, there was no treatment effect in nondiabetics. It is pathobiologically plausible that inhibition of platelet aggregation would be particularly important in diabetics. However, as noted, many other comorbidities aggregate in diabetics and, because this was a univariate analysis, it would be premature to deny nondiabetics GP IIb/IIIa inhibitors.[125]

The advantages of an integrated approach to risk stratification also hold true for therapeutic decision making. Using the TIMI Risk Score for UA-NSTEMI to categorize patients, a gradient of benefit has been demonstrated for the use of LMWH, GP IIb/IIIa inhibitors, and an early invasive strategy. In TIMI 11B and ESSENCE, treatment with the LMWH enoxaparin had a similar effect as treatment with UFH in patients with a risk score of 0 to 2, conferred a 17% relative risk reduction ($P = 0.016$) in patients with a risk score of 3 or 4, and conferred a 25% relative risk reduction ($P = 0.0025$) in

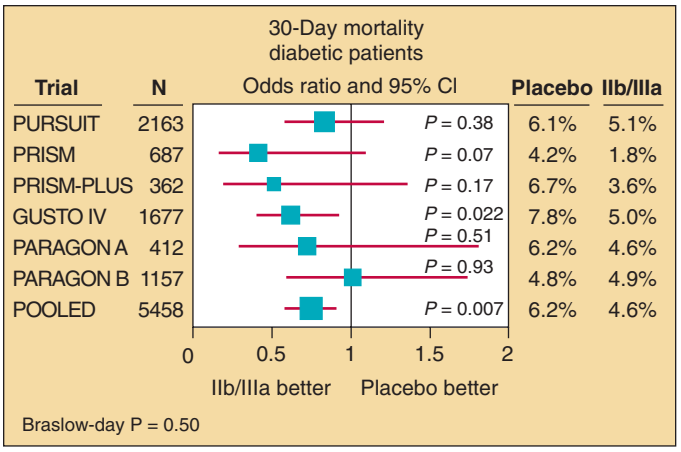

FIGURE 18–10 Odds ratios and 95% confidence intervals for treatment effect of GP IIb/IIIa inhibitors on 30-day mortality in diabetic patients in six trials of GP IIb/IIIa inhibitors in UA-NSTEMI. *(From Roffi M, Chew DP, Mukherjee D, et al: Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non–ST-segment elevation acute coronary syndromes. Circulation 2001;104:2767.)*

patients with a risk score of 5 to 7 ($P_{interaction} = .02$; Fig. 18-11).[30] As the TIMI Risk Score increases, the absolute and relative risk reductions in the composite end point seen with enoxaparin increase, and consequently the number needed to treat to prevent one event decreases.

Similarly, in PRISM-PLUS, treatment with the combination of the GP IIb/IIIa inhibitor tirofiban and UFH had a similar effect as treatment with UFH alone in patients with a risk score of less than 4, but conferred a 34% relative risk reduction ($P = .016$) in patients with a risk score of 4 or higher ($P_{interaction} = .05$; Fig. 18-12).[126] Subgroup analyses from the GP IIb/IIIa inhibitor trials in UA-NSTEMI have suggested that the benefit of GP IIb/IIIa inhibition occurs primarily in patients who undergo percutaneous intervention (PCI). However, not only are these analyses potentially confounded by the fact that patients who undergo revascularization during their index hospitalization tend to be a sicker group, but the implications are less than practical, because the decision to undergo revascularization may occur relatively late in the patient's hospital course. Instead, when patients are stratified by their baseline TIMI Risk Score, those with a risk score of 4 or

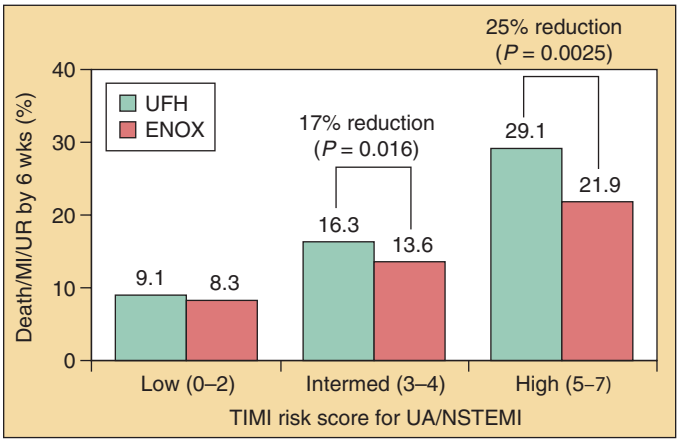

FIGURE 18–11 Death (D), myocardial infarction (MI), or need for urgent revascularization (UR) through 6 weeks by TIMI Risk Score and randomized treatment arm in the combined TIMI IIB and ESSENCE meta-analysis. ENOX, enoxaparin; UFH, unfractionated heparin. *(Data from Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835-842.)*

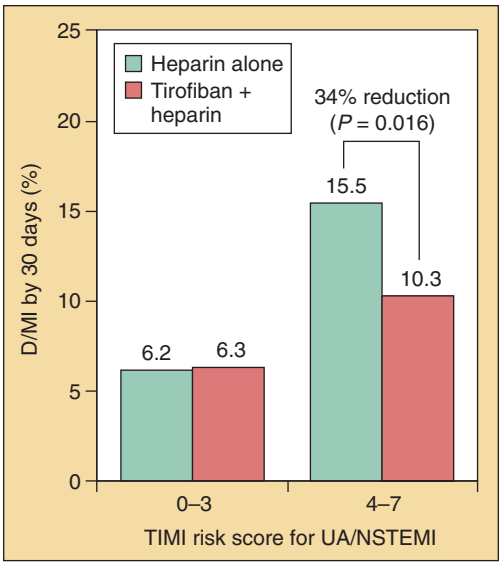

FIGURE 18–12 Death (D) or myocardial infarction (MI) through 30 days by TIMI Risk Score and randomized treatment arm in the PRISM-PLUS trial. *(Data from Morrow DA, Antman EM, Snapinn SM, et al: An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA-NSTEMI in PRISM-PLUS. Eur Heart J 2002;23:223-229.)*

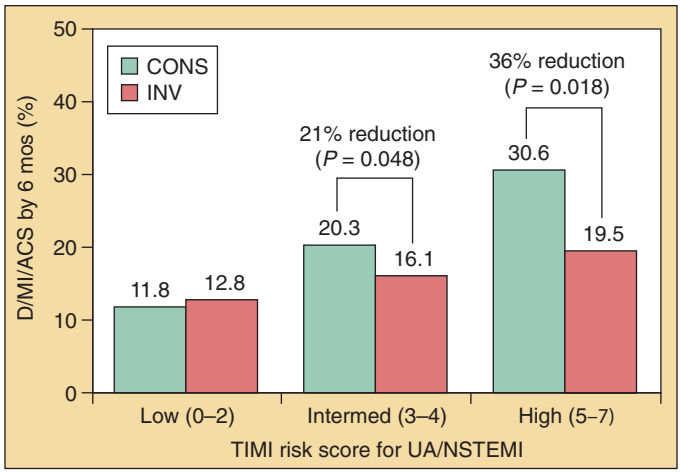

FIGURE 18–13 Death (D), myocardial infarction (MI), or rehospitalization for an acute coronary syndrome (ACS) through 6 months by TIMI Risk Score and randomized treatment arm in the TACTICS-TIMI 18 trial. CONS, conservative strategy; INV, invasive strategy. *(Data from Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-1887.)*

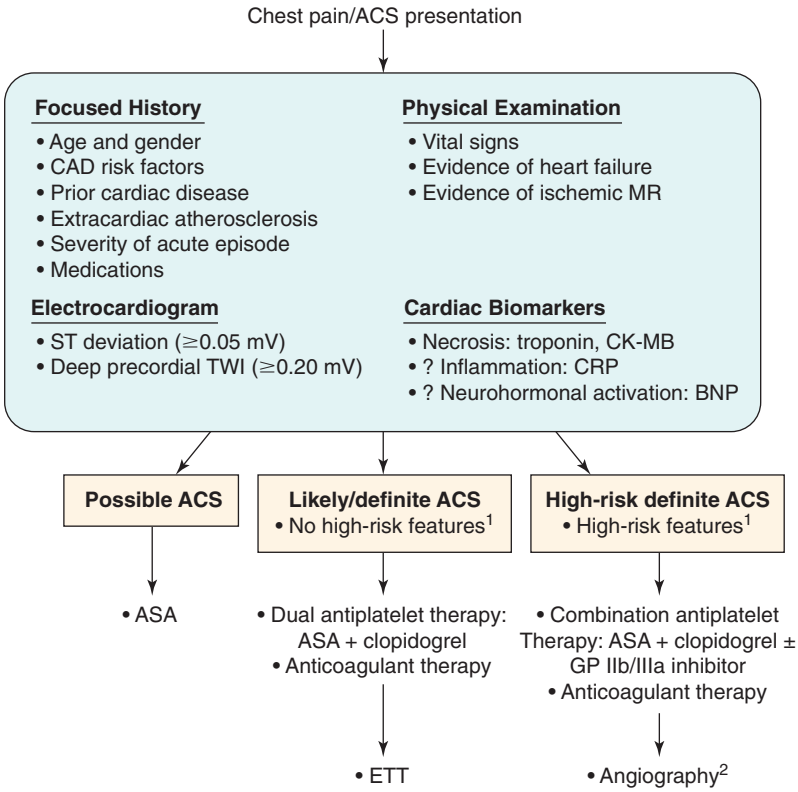

FIGURE 18–14 Algorithm for risk stratification and treatment decision in patients with non–ST-elevation acute coronary syndromes. [1]High-risk features include elevated cardiac troponin level, new or presumably new ST-segment depression, signs of heart failure or worsening mitral regurgitation, reduced left ventricular function (LV ejection fraction less than 40%), hemodynamic instability, or a high risk score (e.g., TIMI, GRACE). [2]Routine angiography should occur within 48 hours.
ASA, aspirin; ETT, exercise tolerance test; MR, mitral regurgitation; TWI, T-wave inversion.

higher who received tirofiban had 25% to 30% relative risk reductions in death, MI, or refractory ischemia, regardless of whether they underwent PCI.[127]

Finally, in TACTICS-TIMI 18, the TIMI Risk Score again defines a gradient of benefit; treatment using an early invasive strategy had a similar effect as treatment with a conservative strategy in patients with a risk score of 0 to 2, conferred a 21% relative risk reduction ($P = .048$) in patients with a risk score of 3 or 4, and a 36% relative risk reduction ($P = .018$) in patients with a risk score of 5 to 7 (Fig. 18-13).[13] Similarly, in the multicenter Canadian registry, non–ST-segment elevation ACS patients with a high GRACE Risk Score appeared to derive particular benefit from in-hospital revascularization (high vs. low group: OR, 10.67; 95% CI, 5.80 to 19.61; $P < .001$).[128]

Algorithm for Risk Stratification and Treatment Decisions

An algorithm for the approach to patients with suspected UA-NSTEMI is presented in Figure 18-14. This approach highlights elements from the recent American College of Cardiology–American Heart Association 2007 guidelines for UA-NSTEMI.[6] A focused history and physical examination, 12-lead ECG, and cardiac biomarker determination provide the critical elements necessary for appropriate risk stratification. Aspirin should be administered to all patients with a presumed ACS, and a thienopyridine to those with likely or definite ACS. For patients in whom a conservative strategy is selected, enoxaparin, fondaparinux, or UFH can be used, with enoxaparin or fondaparinux being preferable to UFH. In patients for whom an invasive strategy is selected, enoxaparin, UFH, bivalirudin, or fondaparinux can be given. GP IIb/IIIa inhibitors and early angiography are used for patients with definite ACS with continued ischemia, high-risk features (including troponin level elevation, ST-segment depression, or high risk score), or when PCI is planned.

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SECTION IV

Management of Acute Coronary Syndromes

CHAPTER 19

Treatment Principles and Emerging Therapies in Acute Coronary Syndromes without ST-Segment Elevation

Pierre Théroux

Atherosclerosis is a multifactorial disease presenting with diverse clinical phenotypes. For example, manifestations range from an elderly patient with few or no symptoms and three-vessel disease, to an asymptomatic individual in his mid-forties dying suddenly from an isolated coronary obstructive lesion.

Not surprisingly, a number of different diagnostic and risk estimate tools and treatment modalities have been developed tailored to the various stages of the disease and risk stratification.

This chapter discusses some concepts, diagnostic tools, and therapies now emerging that could become part of tomorrow's practice. The long-term aim in treatment of coronary artery disease (CAD) eradication of its malignant aspects of death and disability which are primarily consequences of acute coronary syndromes.

LIFESTYLE ADJUSTMENT FOR THE PREVENTION OF ACUTE CORONARY SYNDROMES

Atherosclerosis is now seen as a largely preventable disease, as dynamic changes are increasingly seen in its epidemiology, clinical manifestations, and prognosis among individuals and societies. Thus, the prevalence of cardiovascular disease became epidemic in the last century, peaking in 1964 to 1965, then steadily declined by up to 50% until now despite a fivefold increase in the proportion of the population aged more than 65 years. The IMPACT statistical model applied to the epidemiologic data obtained between 1980 and 2000 could attribute 47% of this reduction to treatment modalities, including secondary preventive therapies after myocardial infarction or revascularization (11%); initial treatments for acute myocardial infarction or unstable angina (10%); treatments for heart failure (9%); revascularization for chronic angina (5%); and other therapies (12%). Another 44% could be attributed to changes in risk factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%).[1] The gain observed during these 2 decades was partially offset, however, by an increase in the body mass index and in the prevalence of diabetes that accounted for an increased mortality rate of 8% and 10%, respectively. These new facets of risk factors are linked to the components of the so-called metabolic syndrome (see Chapter 1), and keep expanding as the prevalence of obesity and associated risk factors including hypertension, dyslipidemia, and diabetes, keep getting higher in adults and children from industrialized and developing countries, particularly in urban settings.[2] The World Health Organization reported that in 2005, approximately 1.6 billion adults (older than 15 years) and 20 million children (aged 5 years or younger) were overweight, and 400 million adults definitively obese. The projections for 2015

BOX 19-1 Risk Factors for Cancer*

- Growing older
- Tobacco
- Sunlight
- Ionizing radiation
- Certain chemicals and other substances
- Some viruses and bacteria
- Certain hormones
- Family history of cancer
- Alcohol
- Poor diet, lack of physical activity, or being overweight

*Many of these risk factors are the same as those for cardiovascular disease, providing an opportunity to impact concomitantly on the two main killers in our society.
(Adapted from the National Cancer Institute, U.S. National Institutes of Health: Cancer Causes and Risk Factors, 2010. Available at http://www.cancer.gov/cancertopics/prevention-genetics-causes/causes.)

are 2.3 billion overweight adults and 700 million obese. These figures may signal a renewed increase in the incidence of coronary artery disease.

Primary prevention is an issue for both society and individuals; it is foremost a lifestyle question. In their task of caring for patients as health specialists, physicians are particularly well positioned to promote prevention in the community. The importance of such interventions is reinforced by the high prevalence of CAD, which still ranks first as the cause of mortality, by the well-documented efficacy of interventions currently available, and by the dynamics of atherosclerosis, the prevalence of which can rapidly shift and plaques rapidly progress and regress in an individual. An optimistic rather than a defeatism approach is better stimulation for patients. As a bonus, it is good to know that lifestyle interventions favorably affect the rates of cancer, the second most frequent cause of death after cardiovascular disease. It is now well documented that cancer and atherosclerosis share very similar risk factors (Box 19-1).

Overlap Between Primary and Secondary Prevention

The driving principles in prevention and treatment of coronary artery disease are first to screen for the disease; second, appreciate the individual degree of risk; and third, apply risk-tailored treatment. Risk is best appreciated by evaluating the presence of traditional and new risk factors helped by appropriate surrogate markers. Two important clues are readily available at first contact with a patient. One is any evidence of atherosclerosis in a vascular region at the medical history or upon clinical examination for example, the presence of a carotid murmur or altered pulse in the lower limbs; the other is the mere presence of a symptomatic disease, which per se carries a worse prognosis than the asymptomatic disease. The measured ankle-brachial pressure index (ABPI) is the ratio of the blood pressure in the lower legs to the blood pressure in the arms, which has 90% sensitivity and 98% specificity for detecting hemodynamically significant stenosis in major leg arteries.

Risk Scores

Based on a half-century of epidemiologic research, the Framingham score has served as reference in the various guideline recommendations and has been instrumental for validating the value of various interventions. This registry was initiated in 1948, when it recruited 5209 men and women aged 30 to 62 years free from cardiovascular disease (CVD) in the town of Framingham, Massachusetts. Five cohorts were subsequently added, the first being the offspring cohort in 1971.[3] The strengths of the score have been well delineated, as well as its weaknesses, which are mainly related to the relatively homogeneous regional population that has been enrolled and the underrepresentation of important subgroups, such as nonwhites, diabetics, and renal failure patients. Many other systems have been developed following the Framingham model to predict cardiovascular disease and coronary heart disease. Major systems were the Joint British Societies' cardiovascular disease risk prediction chart,[4] the Cardio Risk Manager (CRM) calculator,[5] the PROCAM risk score (using triglyceride levels and the presence of diabetes and a family history of premature myocardial infarction in addition to the Framingham criteria),[6] the UKPDS risk engine, looking more specifically at diabetic patients,[7] the HeartScore (Systematic Coronary Risk Evaluation) system of the European Society of Cardiology,[8] and the QRISK study. The HeartScore includes 12 European cohort studies, 250,000 patients, 3 million person-years of observation, and 7000 fatal cardiovascular events recorded; its goal was to define from lifestyle and risk factor data, the therapeutic targets for CVD prevention focusing mainly on mortality prediction. The first QRISK (QRISK1) study was the largest risk prediction study; it was generated by retrospectively extracting data on traditional risk factors and indicators of social deprivation, family history, antihypertensive treatment, and subsequent cardiovascular events in almost 2 million people from the QRESEARCH primary care database, covering about 7% of the population of the United Kingdom.[9]

Markers as Diagnostic Aids

It has become popular to validate potentially useful new markers in primary prevention by determining how they can sharpen risk stratification based on the Framingham score. The coronary artery calcium score was found useful to predict risk in individuals with a Framingham score associated with a 10-year event rate greater than 10% ($P < .001$) but not in those with a risk of less than 10%.[10] Note that the calcium score should not influence the management of patients presenting to the emergency department with chest pain. In a subset of 175 patients who participated in the Multi-Ethnic Study of Atherosclerosis (MESA) trial who underwent coronary angiography, primarily because of chest pain, 7 patients (4%) had significant coronary obstruction despite having a coronary artery calcium (CAC) score of 0 at baseline. The CAC score can miss soft plaques, which play an important role in acute coronary syndrome (ACS); its low negative predictive value does not provide sufficient reassurance and mandates the use of other diagnostic methods for ischemia detection in symptomatic patients.[14] The usefulness of the score was also documented in various ethnic groups.[11] It was found with the Reynolds score that adding serum levels of high-sensitivity C-reactive protein and the presence or absence of a family history of CVD before age 60 years could improve the prognostic value of the Framingham score in healthy men and women in a low- to moderate-risk category.[12] In one study, the measure of brachial artery flow–mediated dilation and the presence of a carotid plaque, but not the maximal carotid intima-to-media ratio, significantly increased the accuracy of the score to predict coronary events, again in subjects with a low to intermediate Framingham score.[13]

Coronary multislice computed tomography (see Chapter 16) provides new windows on heart anatomy and function including coronary arteries. In a study of 295 patients (61% men; mean age, 54 ± 13 years) with no known CAD, stenoses greater than or equal to 50% in one or more epicardial coronary arteries were found in 16%, 34%, and 88% of individuals classified at low, intermediate, and high Framingham score, respectively; proximal calcified or noncalcified plaques in the left main or proximal left anterior descending artery

were found in 44%, 75%, and 63% of patients, respectively, showing that a significant proportion of individuals with a low to intermediate Framingham risk score can still have obstructive CAD.[15] Such improvements in the discriminatory value of the Framingham score by various approaches may not be surprising, especially in the intermediate-risk category. Tests that have been shown to sharpen the diagnostic ability of the Framingham score include exercise testing (see Chapter 13), blood markers of hemostasis (e.g., fibrinogen, D-dimer, plasminogen activator inhibitor-1 [PAI-1] activity, factor VIIc) and of inflammation (e.g., interleukin 6, C-reactive protein [CRP]) and endothelial dysfunction (e.g., P-selectin, von Willebrand factor), and metabolic and renal function markers, including albuminuria.[16,17]

The 2009 Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult suggest the use of high-sensitivity CRP in men older than 50 and women older than 60 years who are at intermediate risk (10% to 19%) by the Framingham score and who do not qualify for statin treatment with low-density lipoprotein (LDL) levels less than 3.5 mmol/L.[18]

IDENTIFYING HIGH-RISK LESIONS

A major challenge in modern cardiology is the recognition of lesions at high risk—the so-called vulnerable plaques—before they provoke the acute coronary syndrome. These culprit lesions have been well characterized in pathologic studies and compared with stable plaques (see Chapter 6); their recognition in vivo would permit innovative research to identify interventions to prevent progression to an ACS and irreversible myocardial damage. Numerous innovative approaches are now being investigated for this purpose (see Chapter 17).

Virtual Histology–Intravascular Ultrasound

Gray-scale intravascular ultrasound (IVUS) imaging permits imaging of the vessel from inside the lumen and provides information on the site, area, volume, and remodeling of the plaque (see Chapter 14). Some of the limitations of IVUS can be overcome by using spectral analysis of the radiofrequency ultrasound backscatter. This technology, called virtual histology-IVUS (VH–IVUS) permits the identification of the fibrous, fibrofatty, dense calcium, and necrotic core components of the plaque (see Chapter 17).[19] Plaques in ACS show a large necrotic and lipid core and thin-cap fibroatheroma, and less fibrotic component than in stable angina.[20] Such rupture-prone plaques in one study were associated with high levels of N-terminal pro-B-type natriuretic peptide (NT–proBNP),[21] providing an explanation for the strong predictive value for mortality of the natriuretic factor (see Chapter 1).

Multislice Computed Tomography

One study compared VH-IVUS and multislice computed tomography (MSCT) in the same patients (Fig. 19-1). With MSCT, 32% of plaques in ACS were noncalcified and 59% were mixed, a third of them having thin-cap fibroatheroma, compared with 61% of plaques calcified in stable angina, with less than 5% having thin-cap. On VH-IVUS, the percentage of necrotic core was higher and thin cap fibroatheroma more prevalent in ACS than in stable angina.[22]

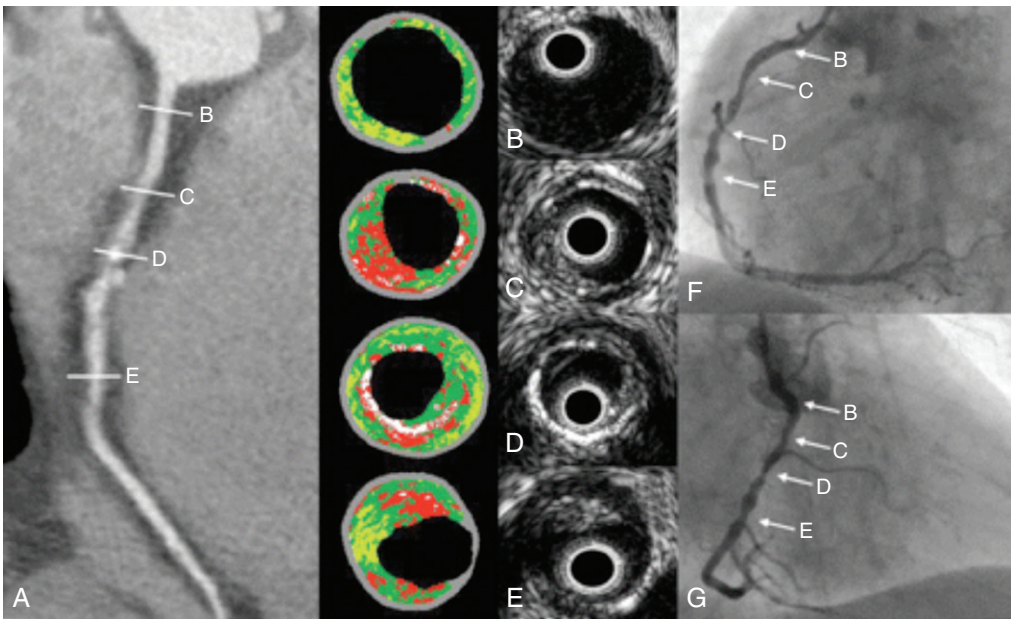

FIGURE 19–1 Coronary plaques in the culprit vessel of a patient presenting with unstable angina pectoris. **A** (left panel), Multislice computed tomography (MSCT) multiplanar reconstruction of the right coronary artery showing obstructive noncalcified and mixed plaques. **B-E** (center panel), Gray-scale intravascular ultrasound (IVUS) images and the corresponding VH (virtual histology) IVUS images. In **B,** a small amount of plaque in the proximal right coronary artery is seen, which appears normal on MSCT. A thin-cap fibroatheroma) with a large amount of necrotic core is detected in proximal and distal noncalcified plaques of the right coronary artery **(C, E)**. A corresponding cross section of a mixed plaque in the mid–right coronary artery shows plaque with calcium on VH-IVUS **(D)**. **F, G** (right panel), Multiple obstructive stenoses in the right coronary artery were confirmed on invasive coronary angiography. VH-IVUS plaque components: dark green fibrotic tissue; light green, fibrofatty tissue; red, necrotic core; white, dense calcium. *(Pundziute G, Schuijf JD, Jukema JW, et al: Evaluations of plaque characteristics in acute coronary syndromes: Non-invasive evaluation with intravascular ultrasound radiofrequency data analysis. Eur Heart J, 2008; 19:2373-2381, with permission.)*

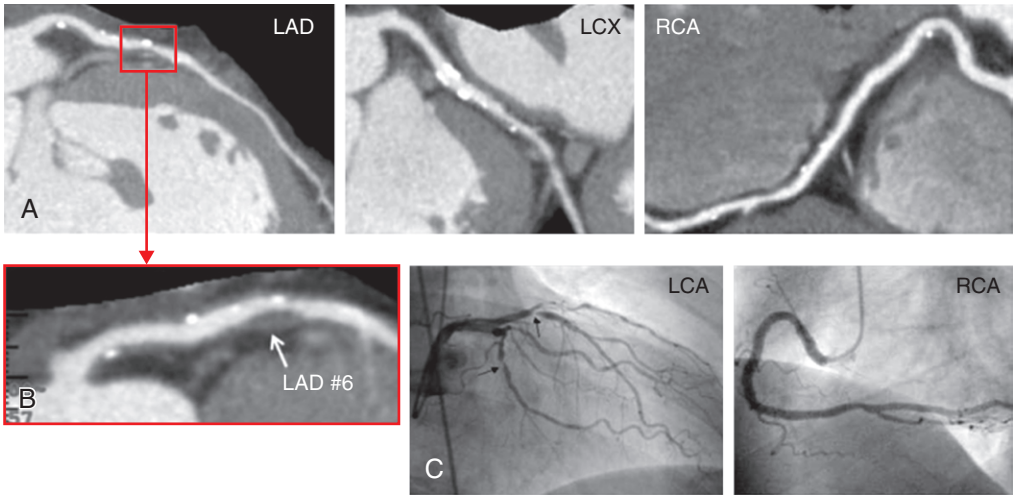

FIGURE 19–2 Identification of a lesion at risk by CT angiography. **A,** Images of left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) in a patient who developed an ACS 6 months later. **B,** Magnification of **A;** the arrow (LAD #6) points to a plaque with positive remodeling, low-attenuation, and spotty calcification. **C,** Invasive coronary angiography after the episode of ACS, identifying the culprit lesion as corresponding to the lesion LAD #6 seen on the CT angiography in **B.** *(From Motomaya S, Sarai M, Harigaya H, et al: Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54;49-57, with permission.)*

Another study prospectively looked at the prognostic value of plaque characteristics at CT angiography in 1059 stable patients followed for 27 ± 10 months.[23] The 45 patients who developed an acute ischemic event showed both positive vessel remodeling and low-attenuation plaques (Fig. 19-2). ACS developed in 22.2% of patients with the two features and in 3.7% of patients with one feature. Only 4 of 820 patients (0.5%) with neither positive remodeling nor low-attenuating plaques developed an ACS. None of the 167 patients with normal angiograms had acute coronary events ($P < .001$). The hazard ratio (HR) for an ACS with one or two plaque features was 22.8 (95% confidence interval [CI], 6.9 to 75.2; $P < .001$).

Lipoprotein-Associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2), as discussed in Chapter 1, is produced by activated inflammatory cells, carried in the circulation bound to LDL cholesterol, and penetrates the plaque core in the vessel, where it produces inflammatory, proapoptotic activity and enzymatic plaque. High expression of Lp-PLA2 is found in human plasma and also in human thin-cap fibroatheroma at a high risk of rupture. These amounts assessed in the carotid plaque of 162 consecutive patients undergoing elective carotid endarterectomy could predict cardiac death and nonfatal acute myocardial infarction in the following 48 months, with above median-levels associated with a more than threefold increase in risk (HR, 3.39; 95% CI, 1.13 to10.17).[24] The data suggest that Lp-PLA2 is a systemic marker of plaque inflammation and vulnerability. This observation and others such as the association between myocardial infarction and inflammatory diseases like rheumatoid arthritis and psoriasis provide a rationale for testing innovative anti-inflammatory and immune modulation therapies (see Chapters 7 and 8).

Darapladib is a novel, selective, reversible, and orally active drug that selectively inhibits plasma and lesion Lp-PLA2 activity. At daily dosages of 40, 80, and 160 mg, darapladib inhibited Lp-PLA2 activity by approximately 43%, 55%, and 66% in patients using atorvastatin.[25] The drug activity on plaque morphologic study was evaluated in 330 patients with angiographically documented coronary disease by comparing the effects of 12 months of treatment with darapladib 160 mg daily or placebo.[26] Whereas darapladibdecreased Lp-PLA2 activity in blood by almost 60%, no drug effects were seen in LDL cholesterol and CRP levels, plaque deformability by IVUS palpography, and total plaque volume. The necrotic core volume, however, increased significantly with placebo while it remained unchanged with darapladib, resulting in a significant treatment difference of 5.2 mm^3 ($P < .012$). It was concluded from this study that darapladib prevents necrotic core expansion, a key determinant of plaque vulnerability. Two placebo-controlled phase 3 trials are now ongoing with darapladib; the STABILITY has completed the enrollment of more than 15,000 patients with chronic coronary heart disease (CHD), and the SOLID-TIMI 52 is enrolling patients with a recent ACS.[27]

High-Sensitivity Cardiac Troponin Assays

The emergence of new generations of highly sensitive cardiac troponin tests is influencing our approach to early diagnosis of myocardial infarction (MI) and to the significance of smaller levels of elevations; more specific and more sensitive markers of cell necrosis are calling for new standards. A recent study looked at such a marker in 3679 patients with stable CAD and preserved left ventricular function previously enrolled in the PEACE trial.[28] The limit of detection of the test used was 0.001 μg/L compared with 0.01 μg/L for the most recent standard test by the same company. The incidence of cardiovascular events during a median follow-up period of 5.2 years was studied. Concentrations of cardiac troponin T were at or above the limit of detection (0.001 μg/L) in 3593 patients (97.7% of the total population) and at or above the 99th percentile for apparently healthy subjects (0.0133 μg/L) in 407 patients (11.1%). After adjustment for other independent prognostic indicators, an elevation of troponin T still strongly correlated with cardiovascular death (adjusted HR per unit increase in the natural logarithm 2.09; 95% CI, 1.60 to 2.74; $P < .001$), and with heart failure (2.20; 95% CI, 1.66 to 2.90, $P < .001$), but not with myocardial infarction. This increased risk with higher levels of troponin

T was evident well below the limit of detection of conventional cardiac troponin T assays and below the 99th percentile of values in a healthy population.

Genomics and Pharmacogenomics

Genomics and pharmacogenomics are primed for expanding clinical applications. Current trends and fields of interest are discussed in Chapter 10, and the poor responsiveness to clopidogrel is detailed in Chapter 21.

The association demonstrated between a polymorphism of the MC2 class transactivator and the susceptibility to develop rheumatoid arthritis, multiple sclerosis, and MI is also of interest for a common immune pathophysiology of chronic inflammation and coronary artery disease.[29]

More recently, a strong support for a causal role of lipoprotein(a)—Lp(a) in coronary disease was determined.[30] The association study was performed in 3145 patients with CAD and 3352 control subjects with replication, and was tested in three independent populations involving 4846 additional patients with CAD and 4594 controls. Two common single-nucleotide polymorphisms (SNPs) in the Lp(a) gene correlating with both CAD and Lp(a) levels could be identified. These SNPs accounted for 36% of the variation in blood levels, with one of six persons being carriers, and for a 1.5-fold increase in the risk of CAD.

TREATMENT

The goals of treatment during the acute phase of an ACS are to preserve life first, and then to protect the ischemic myocardium to maintain left ventricular function and quality of life. Concomitantly, a secondary prevention program is progressively implemented and individualized to patients.

Tools available to achieve these goals have considerably improved over the last decades from a pharmacologic, procedural, and educational perspective. There exist now options to select an antiplatelet and antithrombotic therapy that is individually tailored to the risk of an ischemic versus a bleeding event. Concomitantly, interventional procedures are becoming increasingly successful and safe.

A number of drugs tested to control the active plaque, such as antibiotics and anti-inflammatory drugs failed to show a benefit (see Chapter 25). Similarly, pharmacologic means to prevent the progression of cell necrosis were unsuccessful in the absence of reperfusion. The cyclooxygenase-2 inhibitors and the nonsteroidal anti-inflammatory agents were found relatively contraindicated as was hormonal replacement therapy in secondary prevention.

Acute-Phase Therapy

ACS is conveniently subdivided into ST-segment elevation MI (STEMI) and non–ST-segment elevation MI (NSTEMI), as the different pathophysiologies mandate a different immediate patient orientation.

ST-Segment Elevation Myocardial Infarction. STEMI is transmural or near-transmural ischemia, and is the consequence of a complete occlusion of an epicardial artery in the absence of coronary collateral blood flow. As soon as flow is interrupted, necrosis appears in the most sensitive subendocardial area and rapidly progresses from the area of subendocardial ischemia to the subepicardial area, as well as laterally, a phenomenon that has been named the wavefront phenomenon of progression in myocardial necrosis.[31] After a few hours and with an exponentional curve, necrosis will cover the area at risk unless reperfusion supervenes to interrupt the process; no other cell protection therapy has been shown useful in humans to prevent this progression in necrosis. Reperfusion can be spontaneous and limit the infarct zone compared with the area at risk. It can also be induced therapeutically by fibrinolytic agents or mechanically by percutaneous-procedure interventions or surgical procedures. The sooner it is achieved, the smaller is the final infarct size, a concept well illustrated by the sayings "time is muscle" and "muscle is life." The myocardial infarction can be aborted if reperfusion is achieved within 45 minutes of severe ischemia, and near-normal ejection fraction preserved with reperfusion successfully achieved within 45 to 120 minutes of ischemia. The gain is not infrequently limited by a no-reflow phenomenon that is the result of endothelial swelling, compression by tissue, myocyte edema, and neutrophil infiltration; this phenomenon is accelerated by reperfusion.[32]

The importance of the timing of reperfusion was confirmed in humans by modern means with nuclear magnetic resonance imaging (NMR), which showed that the time to reperfusion was the main determinant of the extent of reversible and irreversible myocardial injury.[33] In NMR studies performed 3 days following successful primary percutaneous coronary intervention (PCI) in 70 patients, mean infarct size increased from 8% to 11.7%, 12.7%, and 17.9%, respectively, ($P = .017$) by higher quartile categories from symptom onset to balloon inflation of 90 minutes, 90 to 150 minutes, 150 to 360 minutes, and greater than 360 minutes. Microvascular obstruction became larger with time, from 0.5% to 1.5%, 3.7%, and 6.6%, respectively, ($P = .047$), while salvaged myocardium markedly decreased from 8.5% to 3.2%, 2.4%, and 2.1% ($P = .004$).

Non–ST-Segment Elevation Myocardial Infarction. The necrosis in NSTEMI is located in the most ischemia-sensitive subendocardial area, and is the consequence of a plaque rupture or erosion that triggered formation of an obstructive thrombus that can be flow-limiting and/or yields distal microembolizations of plaque debris and thrombotic material (see Chapter 6). Small areas of myocardial necrosis are then created, named micro-infarcts, and are often precipitated by PCI. The negative prognostic value of such small infarcts has been well documented. Diagnosis is then based on an elevation of cardiac troponin levels, as the marker is highly sensitive and specific to detect cell necrosis; creatine kinase, MB fraction (CK-MB) has been better validated with intervention-related MI and is usually based on a threefold elevation above the normal values. A chest pain that lasted more than 20 to 30 minutes with ST-T changes is also strongly positive. Other diagnostic helps are focal systolic or diastolic dysfunction on the echocardiogram, a fixed flow-deficit on the nuclear scan, and late enhancement on NMR.

Drug Therapy and Procedures

In STEMI, restoration of an effective forward flow is essential to prevent death and minimize the extent of irreversible myocardial damage. Therefore, primary PCI is preferred treatment whenever it can be done within the recommended time window, as it more rapidly and reproducibly restores full blood flow. Reperfusion during that golden hour that follows the onset of pain can abort the infarction. In NSTEMI, the treatment priority is prevention of recurrent microembolization and microinfarcts and/or of an abrupt complete coronary occlusion leading to STEMI.

PCI in both STEMI and NSTEMI helps reduce the thrombogenicity of the plaque and prevent coronary reocclusion and infarct extension by breaking the thrombogenic plaque and thrombus, and by opening the lumen thus reducing the high shear rate that provokes platelet aggregation.

Anticoagulant and dual- or triple-antiplatelet therapy is required acutely, and dual antiplatelet therapy is prescribed in the following months to prevent rethrombosis and acute or subacute stent thrombosis if a stent was implanted. A potential additional long-term gain by adding orally active

factor Xa and thrombin inhibitors is now under investigation in numerous phase 3 trials. Inhibitors of the platelet thrombin receptor PAR-1 are also being investigated.

The various options presently available in the selection of antiplatelet and anticoagulant drugs for an optimal risk/benefit ratio are discussed in Chapters 20 and 21, respectively; specific modalities for most patients referred for PCI are presented in Chapter 28.

Timing of Interventions. The best timing for performing interventional procedures was undetermined until recently. The initial randomized trials and observational studies that compared early versus delayed intervention in general reported a hazard of death or myocardial infarction with early interventions. No such hazard was shown in modern trials and studies, likely because of better procedures and stenting. The Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) study randomized 3031 patients with non–ST-segment elevation ACS to routine early intervention with coronary angiography within 24 hours after randomization, or delayed intervention with coronary angiography 36 hours or more after randomization.[34] The primary outcome of death, MI, or refractory ischemia at 6 months occurred in 9.6% of patients in the early intervention group, compared with 11.3% in the delayed intervention group (HR, 0.85; 95% CI, 0.68 to 1.06; $P = .15$). A prespecified analysis showed that early intervention improved the primary outcome in the one third of patients who were at highest risk as evaluated by the GRACE score, but not in the two thirds of patients at low to intermediate risk.

The Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) study randomized 352 patients with a non–ST-segment elevation and a TIMI score greater than 3 to immediate (1.2 hours from randomization to sheath insertion) or next-day catheterization (mean, 20.5 hours). PCI was performed with triple-antiplatelet therapy with a radial access in 84% of patients, and a drug-eluting stent in 52%.[35] The primary end point consisting of peak troponin levels during hospitalization did not differ between the two strategies. The secondary outcome, a composite of death, MI, or urgent revascularization at 1-month follow-up, was observed in 13.7% of the group assigned to immediate intervention and in 10.2% of the group assigned to delayed intervention ($P = .31$). The other end points, as well as major bleeding, did not differ between the two strategies.

Thus, the best data available suggest that percutaneous interventions can be safely delayed 24 to 48 hours after admission, and that the very high risk patients benefit from an accelerated procedure with no increased risk.

Statin Therapy. Beyond their long-term benefits, statins have emerged as potentially useful drugs in the short-term in ACS and in interventional procedures. The exact mechanisms are unclear but likely pertain to their favorable pleiotropic effects on inflammatory, thrombosis, and the oxidative stress. The landmark PROVE-IT study randomized 4162 ACS statin-naïve patients with total cholesterol levels less than or equal to 240 mg/dL (6.21 mmol/L) or statin-users with cholesterol less than or equal to 200 mg/dL (5.18 mmol/L) to pravastatin, 40 mg OD, or atorvastatin 80 mg, within 10 days of hospital admission. The rate of primary end point (all-cause mortality, MI, unstable angina requiring hospitalization, PCI or coronary artery bypass grafting [CABG], or stroke) during a mean follow-up of 24 months was reduced by 16% with atorvastatin (22.4%) vs. 26.3. Among the subset of 2868 patients who underwent PCI just prior to enrollment, the composite end point was reduced 22% (6.5% to 21.5%, $P = 0.002$).[36] Based on these results, numerous observational studies and a few randomized trials studied the potential benefit of administratering statin therapy up-front, before CABG, PCI, and noncoronary vascular surgery. In one meta-analysis of 18 studies (2 randomized trials, 15 cohort studies, and 1 case-control; CABG in 4 studies, noncardiac vascular surgery in 12 studies, and various other interventions in 2 studies), the statin reduced perioperative death or ACS (odds ratio [OR] reductions 0.26; 95% CI, 0.07 to 0.99) in randomized trials; and OR 0.70; (CI, 0.57 to 0.87) in cohort studies.[37] Another meta-analysis that included 19 studies (3 randomized trials, 16 observational studies) and 31,725 patients, all undergoing cardiac surgery, use of preoperative statin in 17,201 patients was associated with a 43% reduction in the odds ratio of all-cause mortality at 1 month (2.2% vs. 3.7%; $P < .0001$). The rates of atrial fibrillation and of stroke were favorably influenced but not that of MI or renal failure.[38]

The putative benefit of statin was investigated in at least eight recent randomized trials enrolling 200 to 800 patients with stable or unstable angina, and looking at end points of MI defined by biomarker elevations, and major cardiac events (MACE). Most trials reported reductions in the range of 21% to 72% in the number of patients developing MI; the reductions in MACE were less reproducible and mainly driven by effects on MI. Benefits were more striking in patients with ACS.

A study of 200 patients with stable angina undergoing elective PCI showed no benefit on perioperative MI following 2-day administration of 80 mg/day of atorvastatin before the procedure compared with immediate catheterization.[39] A reloading with atorvastatin with 80 mg 12 hours and 40 mg before the intervention in 383 patients with stable angina (53%) or NSTEMI (47%) on chronic statin therapy in the ARMYDA-RECAPTURE trial reduced the end points of 30-day rates of cardiac death, MI, or unplanned revascularization compared with placebo in ACS patients (3.3% vs.14.8%, $P = .015$), but not in stable patients (4% and 4.9%); there were significant interactions for a significant interaction between clinical syndrome and impact of atorvastatin reload.[40] On the other hand, the NAPLES II trial showed a benefit of a single dose of atorvastatin, 80 mg, administered the day before an elective PCI in 668 statin-naïve patients as well as a reduction in periprocedure MI (9.5% vs. 15.8% for controls ($P = .014$).[41] Rosuvastatin 40 mg administered before PCI in 445 consecutive patients with ACS was associated with a significant reduction in the number of periprocedural myocardial injuries (11.4% vs. 5.8%; $P = .035$).[42] A randomized Chinese study in 228 patients with ACS showed significantly better myocardial blood perfusion, less myocardium ischemic injury, and lower levels of hs-CRP, P-selectin, and intercellular adhesion molecule 1 (ICAM-1) with simvastatin, 80 mg for 7 days before the procedure, compared with simvastatin, 20 mg before the procedure.[43]

Other Therapeutic Targets. Anti-ischemic drugs classically address the correction or prevention of myocardial ischemia by promoting oxygen delivery with vasodilators such as nitrates and calcium antagonists, and/or reducing myocardial oxygen needs with beta blockers (see Chapter 23). Innovative drugs and devices are now available investigating new therapeutic targets, as well as cell therapy (see Chapters 27 to 30), increasing our therapeutic options.

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CHAPTER 20

Antiplatelet Therapy

Richard C. Becker, Jens Lohrmann, and Paul Gurbel

The management of patients with acute coronary syndrome (ACS), whether in the initial or later stages of disease, is rooted firmly in three fundamental pathobiological constructs—atherosclerosis, thrombosis, and vascular repair. This chapter summarizes current knowledge of platelets and their pivotal role in ACS with particular emphasis on clinical phenotypes, the evolution of targeted pharmacotherapy, and management strategies for optimizing patient care.

FUNDAMENTAL PLATELET BIOLOGY

Hemostasis and pathologic thrombosis, both platelet and tissue factor-mediated events with life-sustaining and life-threatening potential respectively, depending on the site of occurrence, coexisting conditions, and presence or absence of fully functional regulatory pathways, are familiar to most clinicians. In contrast, platelet biology, including emerging evidence for distinct functional platelet populations and platelet-dependent paracrine effects, represents an opportunity for expanded understanding and translatability from the bench to the bedside.[1]

Megakaryocytes

Platelet production begins with a common hematopoietic stem cell (reviewed in reference 1), from which two distinct blood cell lines emerge—lymphoid (all types of leukocytes) and myeloid (erythrocytes and platelets). Polypoid megakaryocytes, regenerating in human bone marrow at a rate of 10^8 cells per day, are the immediate progenitors of platelets (Fig. 20-1). Each megakaryocyte can, in turn, generate more than 500 platelets. The production of such a large number of cells at a rapid rate represents a teleologic advantage for hemostatic challenges.

Under the influence of thrombopoietin—a protein synthesized in the kidney, liver and bone marrow stroma—megakaryocytes undergo dramatic morphologic changes during a 4- to 10-hour process of platelet production. The sequence of events includes cytoplasmic pseudopod development, proplatelet formation, and release or "budding off" of platelets. In addition to thrombopoietin, megakaryocytes contain both proapoptotic and antiapoptotic factors that collectively serve as biological "thermostats" for the highly regulated transition from proplatelets to platelets.[2,3]

Several proteins of physiologic relevance are selectively expressed during specific phases of platelet development. Commitment of myeloid precursors to the megakaryocyte cell line is indicated by the expression of CD61 (ß3) and increased CD41 expression.[4] Expression of protease-activated receptors (PARs) is determined during megakaryocyte differentiation and maturation.[5] Expression of $\alpha_{IIb}/ß_3$, preceding that of glycoproteins Ib, V and IX, may play a pivotal role in proplatelet formation and release.[6] Similarly, purinergic G protein–coupled P2Y 12 (P2Y12) receptors may also participate in early megakaryocyte development.

Platelet Populations and Subpopulations

Early clotting assays, which relied on platelet-rich plasma preparations, were characterized by considerable patient-to-platelet variability—a hint of things to come in the evolution of our understanding of platelet biology. The early work of Buckwalter, Blythe, and Brinkhous[7] identified patient-specific variability in thrombin generation on platelet surfaces. Subsequent observations made by Bouchard and coworkers,[8] Brummel and associates,[9] and Monroe[10] established the presence of individual differences in platelet activation, factor X binding, factor V binding, conversion of factor X to factor Xa and prothrombinase-mediated thrombin generation.

Recently, it has become increasingly clear that platelet functionality may not only differ between individuals, but within individuals as well—and not only within individuals but within developing clots themselves. Munnix and colleagues investigated the commitment of platelets to forming aggregates and stimulating coagulation—two highly specialized and distinct steps

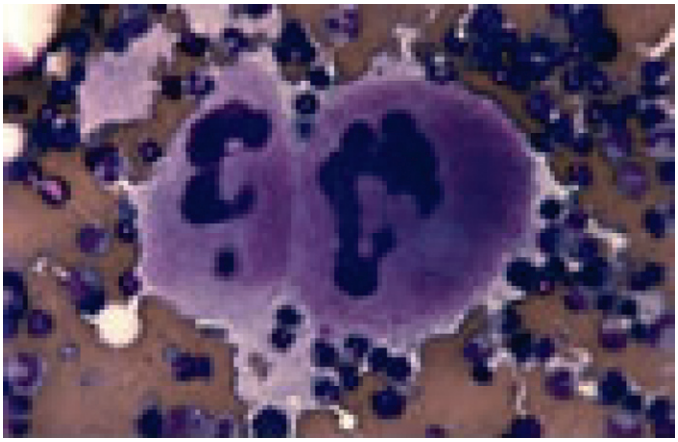

FIGURE 20–1 The polypoid megakaryocytes, or product of myeloid stem cells originating in bone marrow, are the primary progenitor of platelets.

in thrombus formation. High-resolution 2-photon fluorescence microscopy revealed separate platelet populations under flow conditions—one consisted of aggregated platelets, while distinct patches of non-aggregated platelets displayed phosphatidylserine expression, increased binding of coagulation proteins, decreased $\alpha_{IIb}\beta_3$ integrins, and reduced adhesion (Fig. 20-2). A third group of platelets covered with serotonin-derivatized proteins, fibrin(ogen), and thrombospondin in association with granular proteins, such as von Willebrand factor (vWF), factor V, and fibronectin were also identified. The observations suggest that distinct clusters of platelets contribute to aggregate formation, while others participate solely in procoagulant activity.

Under normal conditions platelets circulate freely without significant interaction with other platelets or healthy vascular endothelium. In the presence of endothelial disruption or activation, whether from vascular injury, rupture of an atherosclerotic plaque or maladaptive signals, a chain of events ensues that leads to platelet-rich clot formation.[11,12] Depending on the initiating event, this may represent protective hemostasis, a vital step toward vascular repair, or pathologic vascular thrombosis causing an acute coronary syndrome or ischemic stroke. The causative events represent a complex series of integrated biochemical and cellular processes that can be divided into five functional categories: translocation (tethering), activation, secretion, adhesion, and aggregation and transformation.

Translocation (Tethering)

Following vascular injury with exposure of subendothelial surfaces, or on activated endothelial cells, platelets move rapidly on bound vWF because of interactions between vWF and the glycoprotein (GP) Ib-IX-V complex.[13] This translocation, or transient arrest, is followed by platelet activation and

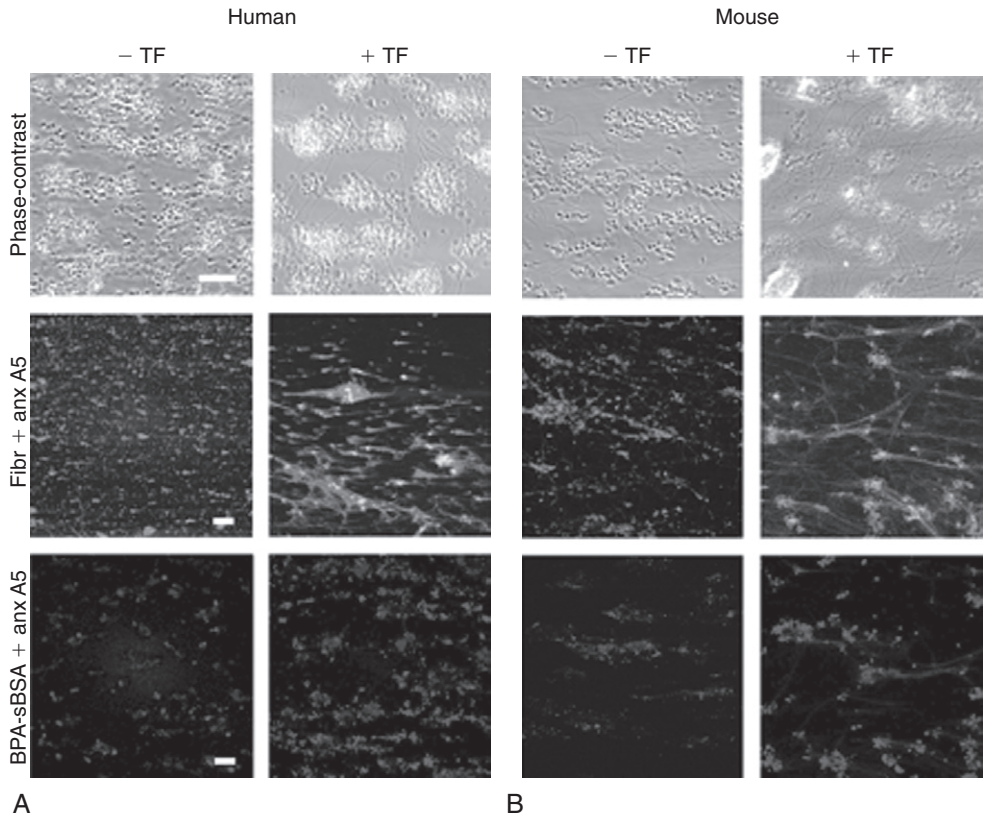

FIGURE 20–2 Heterogeneity in human and murine thrombi formed on collagen. Flow experiments were performed with human **(A)** or murine **(B)** blood in the absence of tissue factor (-TF) using PPACK-anticoagulated blood (left citrate blood that was perfused together with tissue factor (+TF, 2 pM, f.c.) and $CaCl_2$ (2 mmol/L free Ca^{2+}, f.c.) to allow coagulation (right columns). Standard perfusion time was 4 minutes at a shear rate of 1000 s^{-1}. Blood was preincubated with 0.2 mg/mL OG-fibrinogen. Alternatively, preincubation was with 50 μg/mL BPA-sBSA and postlabeling with 1 μg/mL AF532-labeled streptavidin. In both cases, AF647-annexin A5 was also present. Upper panels, Bright-field phase-contrast images after perfusion. *Middle panels*, TPLSM images of OG-fibrinogen (green) and AF647-annexin A5 (red) fluorescence (different fields of view). *Lower panels*, TPLSM images of BPA-sBSA (blue) and AF647-annexin A5 (red) staining. Images are representative of 4 to 8 experiments; bars indicate 20 μm. *(From Munnix ICA, Kuijpers MJE, Auger J, et al. Segregation of platelet aggregatory and procoagulant microdomains in thrombus formation: Regulation by transient integrin activation. Arterioscler Thromb Vasc Biol 2007;27:2484-2490, with permission.)*

ultimately tethering or arrest on the vascular wall through interaction of $\alpha_{IIb}\beta_3$ integrins with adhesive ligands including fibronectin, fibrinogen, and vWF (described in greater detail under Adhesion).[13]

Activation

In vivo, platelet activation is typically initiated by collagen and thrombin; however, the binding of vWF to GPIb provokes platelet activation and subsequently leads to the activation and expression of $\alpha_{IIb}\beta_3$ on the platelet surface.[14] Under static conditions, collagen can capture and activate platelets without need for cofactors, but under flow conditions, such as those encountered within the coronary vascular bed, vWF is typically required. Four receptors participating in collagen binding have been identified on the surface of human platelets; two bind directly to collagen $\alpha_2\beta_1$ and GPVI, the other two bind collagen via collagen-bound vWF ($\alpha_{IIb}\beta_3$ and GPIb.[15,16] Two separate thrombin receptors have been identified on the platelet surface—a high-affinity receptor known as GPIbα and a moderate-affinity receptor known as the thrombin receptor.[17,18] Thrombin interacts with at least two sites on the thrombin receptor and cleaves the amino-terminal extension to expose a new amino terminus which acts as a tethered ligand, activating platelets by binding to a specific region on the same receptor.[19] Activation by collagen or thrombin produces a platelet monolayer that supports further thrombin generation and the subsequent adhesion of activated platelets to each other.

Concomitant activation of platelets with both collagen and thrombin yields a population of coated (collagen and thrombin-activated) platelets that are enriched in several membrane-bound, procoagulant proteins including thrombospondin, factor V, fibronectin, fibrinogen, and vWF.

The existence of coated platelets is important for several reasons. First, it emphasizes the dynamic nature of platelet activation, which differs according to the agonist(s) involved and local conditions. Second, it underscores that platelet activation is not an "all or none" phenomenon. Third, it highlights the rapidly evolving field of platelet biology with varying populations of cells possessing distinct properties for activation, aggregation, coagulation, protease assembly, and paracrine effects.[20]

There are three main pathways of platelet activation: (1) activation of phosphatidylinositol-4,5-bisphosphate (PIP_2) and second messenger-mediated increase in cytosolic Ca^{2+} concentration (resulting in integrin activation and thromboxane A_2 synthesis) and protein kinase C (resulting in protein phosphorylation); (2) activation of monomeric G proteins in the Rho and Rac families vital to platelet shape change, reorganization of the cytoskeleton, and microparticle formation; and (3) suppression of cyclic adenosine monophosphate (cAMP) synthesis by adenyl cyclase to release a protective mechanism against unnecessary platelet activation.[21]

Secretion

Platelet activation prompts cytoskeleton rearrangements, membrane fusion, and secretion of contents from three different types of platelet storage granules: lysosomes, α-granules, and dense bodies. The lysosomes contain a number of acid hydrolases (cathepsins) that digest endocytosed materials and secretion occurs more slowly than does dense body or α-granule secretion.[22-24]

The platelet α-granules are spherical bodies (300 to 500 nm in diameter) that contain platelet-specific proteins such as platelet-derived growth factor (PDGF), proteins involved in fibroblast proliferation such as connecting tissue activating peptide III (CTAP III) and the heparin neutralizing small protein platelet factor-4.[25-27] Additionally, platelet α-granules contain a number of coagulation proteins including 20% to 25% of factor V. It has been demonstrated that platelet factor V is the major protein secreted and phosphorylated following α-thrombin stimulation.[28,29] Accordingly, platelet factor V is critical to the assembly of prothrombinase, which then generates additional thrombin. Alpha granules also contain protein S (the cofactor for protein C-mediated factor V and VIII inhibition)[30]; plasminogen activator inhibitor-1, which plays a contributing role in modulating local fibrinolytic potential[31]; and fibrinogen. Although meager in comparison with plasma levels, platelet fibrinogen is more highly concentrated, suggesting further that platelets provide a site for localizing hemostatic responses.[32]

The platelet also contains a small number of electron-dense granules, referred to as dense bodies. They contain a large amount of nonmetabolic purines (adenosine diphosphate [ADP], guanosine diphosphate [GDP]) as well as divalent cations (Ca^{2+}, Mg^{2+}), serotonin, and pyrophosphates. ADP secretion following platelet activation promotes recruitment and activation of additional platelets to the site of vascular injury.[22]

Adhesion

Activated platelets adhere strongly to damaged, disrupted, or dysfunctional vascular endothelial cells. This is especially true in areas of exposed subendothelial collagen, lipid deposits and tissue factor, as found in eroded or ruptured atheromatous plaques. Initial coverage of the exposed site by platelets is mediated by several adhesive proteins that are recognized by specific platelet membrane glycoproteins (Table 20-1). There is considerable redundancy and functional overlap, as several receptors may bind the same ligand and a specific receptor may respond to more than one ligand. Platelet surface receptors also include integrins. In contrast to transient adhesion, stable adhesion of platelets to subendothelial tissues requires binding of GPVI and integrin $\alpha_2\beta_1$ to collagen with augmentation provided by glycoprotein (GP) IIb/IIIa $\alpha_{IIb}\beta_3$), to immobilized vWF and fibrinogen, as well as binding of fibronectin to integrin $\alpha_5\beta_3$.[33] Under very high shear stress (>10,000 S^{-1}), activation-independent platelet aggregation mediated by soluble vWF facilitates adhesion and precedes stable aggregation.[34]

TABLE 20–1 Surface Membrane Glycoproteins and Their Associated Ligands

Receptor	Ligand	Integrin Components	Biological Action
GPIa/IIa	Collagen	$\alpha_2\beta_1$	Adhesion
GPIb/IX	von Willebrand factor		Adhesion
GPIc/Iia	Fibronectin	$\alpha_5\beta_1$	Adhesion
GPIIb/IIIa	Collagen	$\alpha_{IIb}\beta_3$	Aggregation (secondary role in adhesion)
	Fibrinogen		
	Fibronectin		
	Vitronectin		
	von Willebrand factor		
GPIV	Thrombospondin		Adhesion
(GPIIb)	Collagen		
Vitronectin	Vitronectin	$\alpha_v\beta_3$	Adhesion
	Thrombospondin		
VLA-6	Laminin	$\alpha_6\beta_1$	Adhesion
GPVI	Collagen		Adhesion

From Becker RC. Platelet surface physiology and its importance in pharmacotherapy design and development: the adenosine diphosphate receptor antagonists. J Thromb Thrombolysis 2000;10:35-53.

An important "end result" of platelet translocation, activation, secretion and adhesion is aggregation, representing a final step toward thrombus growth and development. Adhesive ligands, primarily fibrinogen and vWF, bind via activated $\alpha_{IIb}\beta_3$ (also known as GP IIb/IIIa) receptors expressed on the surface membranes of adherent platelets. In a high shear-stress environment, the "bridging" effect of fibrinogen, which is required for stable platelet plug formation, occurs only after an initial tethering of vWF and GPIbα.[35]

Though vWF and GP IIb/IIIa-mediated platelet aggregation can occur independently of platelet activation, it does so only within areas of very high shear stress, and typically yields an unstable aggregate.[13] Accordingly, a pharmacologic approach to platelet inhibition that focuses on platelet activation (to one or more agonists of relevance through one or more key receptors) has the most sound and biologically-based rationale.

Platelet Autocrine and Paracrine Properties

Platelet-mediated thrombosis is the end result of a well-characterized series of events that include platelet translocation, activation, secretion, adhesion, and aggregation. While each step is vital to the overall process, platelet secretion represents a highly relevant component for two reasons. First, it is responsible for several sustaining autocrine circuits (Fig. 20-3). Second, secretion is responsible for platelet-mediated paracrine effects that contribute to cellular proliferation and vascular repair, among other things.

The importance of understanding fundamental platelet biology, from the perspectives of hemostasis and thrombosis and vascular repair, must not be underestimated. The development of increasingly potent platelet-directly therapies, and a more widely prevalent trend in clinical practice to continue therapy for years at a time, introduces the potential for not only cumulative hemostatic challenges but a new category of vascular disorders, stemming from drug-mediated alterations in physiologic vascular repair.

Arterial Thrombosis Phenotype in Acute Coronary Syndrome

The development of flow altering blood clots is a distinguishing feature in ACS and requires an integrated series of events that involve tissue-factor–bearing clots, platelets, and coagulation proteins.

A cell-based model of coagulation[36] establishes a physiologic, integrated, and functional view of complex biochemical events occurring on cellular (or other biological) surfaces, rather than distinct and relatively independent cascades that may be operational in static fluid systems (Fig. 20-4). It also provides a scientific foundation for understanding the importance of specific platelet binding sites for coagulation proteases,[10,37] the nonhemostatic roles of coagulation factors (which include vessel wall inflammation and cellular proliferation), the dynamic nature of cellular interactions, and the inter-individual variability of platelet procoagulant activity (and thrombotic potential).

According to the cell-based model of coagulation, initiation takes place on intact cells or cellular fragments (monocytes, macrophages, neutrophils, activated endothelial cells, smooth muscle cells, apoptotic cells, platelet microparticles, circulating vesicles) bearing the transmembrane glycoprotein tissue factor.[38] Exposed tissue factor binds and fully activates coagulation factor (f) VII, which subsequently activates fIX and fX (which then activates fV), generating a small amount of thrombin from prothrombin (fII). In the priming or amplification phase, surface-bound thrombin activates platelets (bioamplification), as well as fV, fXI, and fVIII (cleaving the latter from vWF). fXIa generates additional fIXa (whose action is accelerated by fVIIIa), whereas fVa accelerates (and amplifies) the action of fXa. During the propagation phase, fIXa binds to activated platelets, causing further fX activation. The complexing of fXa and fVa to membrane surfaces leads to a

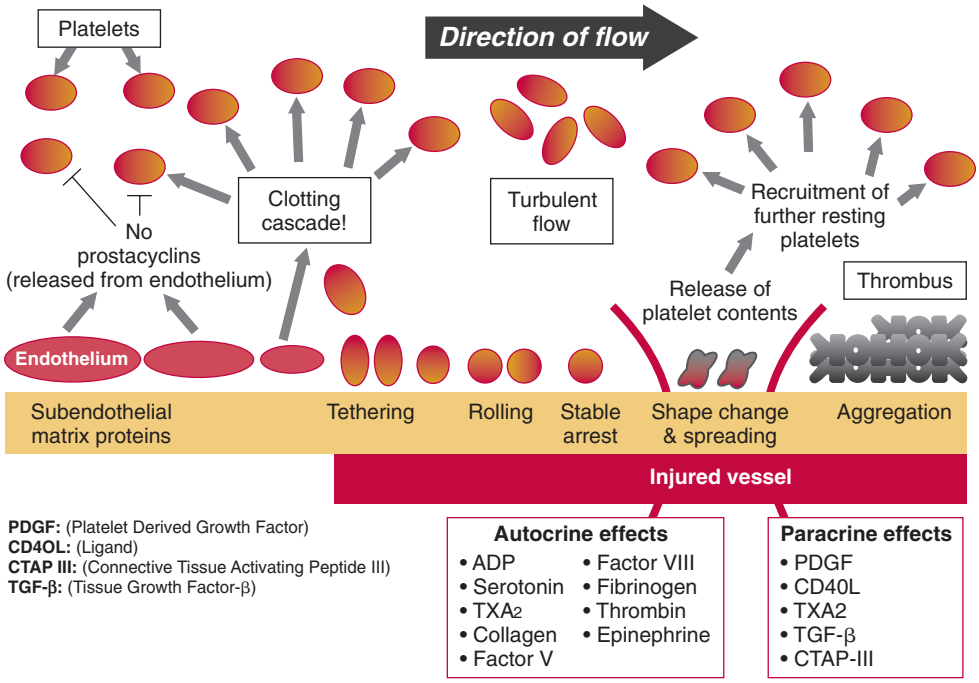

FIGURE 20–3 The vascular surface-centered sequence of events for platelets includes tethering, rolling, arrest (adhesion), shape change-spreading, activation, secretion and aggregation. The release of platelet contents provokes and facilitates autocrine and paracrine effects, respectively. *(From Becker RC: Platelet biology for the clinician-scientist: An evolution of understanding. J Thromb Thrombolysis 2008;25:253-237.)*

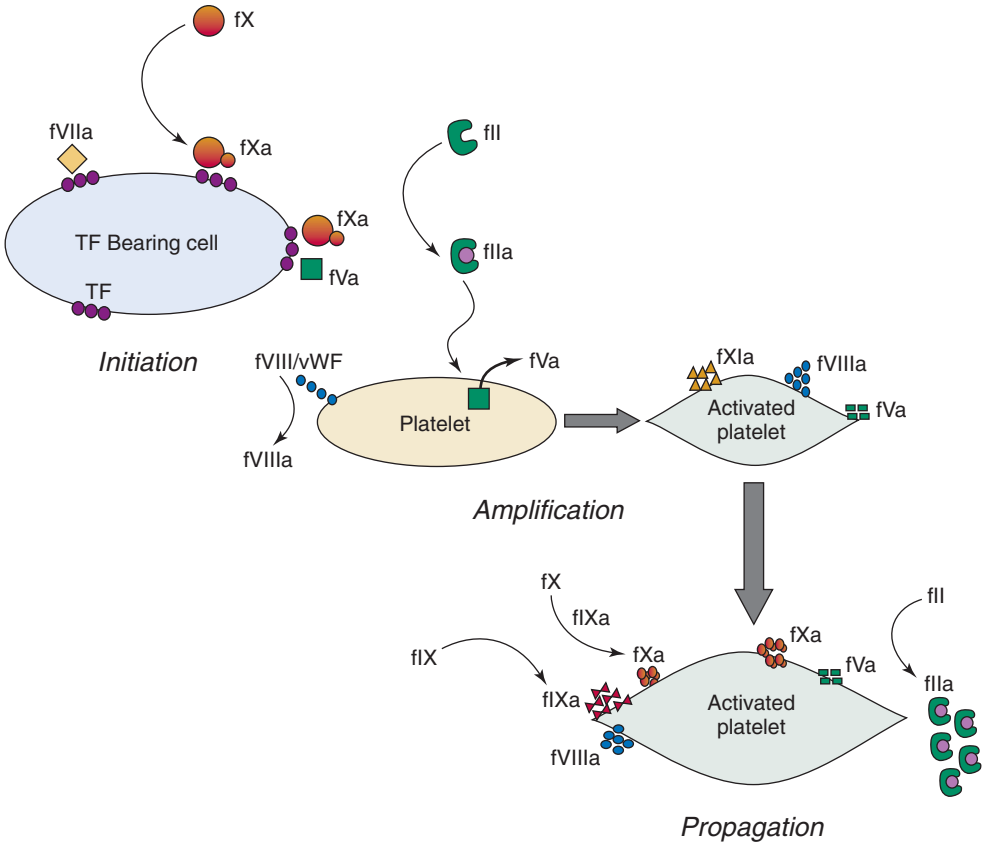

FIGURE 20–4 The cell-based model of coagulation highlights the initiation of events on tissue-factor bearing cells, followed by an amplification step wherein events transition to activated platelets. The propagation state is characterized by a burst of thrombin generation. *(From Hoffman M: A cell-based model of hemostasis. Thromb Haemost 2001;85:958-965.)*

burst of thrombin generation. Thrombin's major hemostatic roles include the conversion of soluble fibrinogen into a tridimensional network of fibrin (coagulation), the activation of platelets through at least two different G protein-coupled PARs[3] (PAR 1 and PAR 4), and the constriction of endothelium-denuded vessels.

Thrombus growth in rapidly flowing blood is closely linked to the presence of soluble and surface-bound vWF.[39] This multimeric protein not only acts as a bridge for the initial tethering and translocation of platelets to subendothelial collagen (via platelet GPIb), but also induces the surface expression of platelet GP IIb/IIIa ($\alpha_{IIb}\beta_3$), leading to the stable adhesion and subsequent aggregation of activated platelets to newly formed and polymerizing fibrin strands.[40]

Termination, elimination, and stabilization of coagulation through cell surface processes are vital for understanding potential dysregulated systems that typify atherothrombotic vascular disease. At least four plasma proteins participate in the initial termination of coagulation: tissue factor pathway inhibitor (TFPI)—released by endothelial cells and platelets, inhibiting tissue factor, fVIIa and fXa; antithrombin III—inhibits thrombin, fIXa, fXa, fXIa, and the fVIIa-tissue factor complex; protein C, a vitamin K-dependent inhibitor of fVa and fVIIIa, activated by the thrombin/thrombomodulin complex; and protein S—a cofactor in protein C-mediated fVa and fVIIIa inhibition. Activated platelets release protease nexin II, an inhibitor of soluble-phase fXIa.[41]

Elimination of fibrin deposits (fibrinolysis) is closely linked to fibrin itself. At the thrombus surface, fibrin attracts plasminogen and tissue plasminogen activator (t-PA) to its lysine residues, whereas single-chain urokinase plasminogen activator (scu-PA) binds to plasminogen. While t-PA converts plasminogen to plasmin, the latter converts scu-PA to urokinase plasminogen (u-PA), which produces additional plasmin from plasminogen.

Stabilization of coagulation counteracts fibrinolysis through thrombin-activated fXIIIa, which converts loosely interlaced fibrin into a tightly knitted aggregate; thrombin-activatable fibrinolysis inhibitor (TAFI), which is activated to TAFIa (when exposed to the thrombin-thrombomodulin complex) and removes lysine residues from fibrin, impairing fibrin's capacity to bind plasminogen and t-PA; plasminogen activator inhibitor type 1 (PAI-1), a rapid and irreversible inhibitor of t-PA and u-PA, released by endothelial cells and platelets; and the high-affinity plasmin inhibitor, alpha-2 antiplasmin.

TRANSLATING PLATELET BIOLOGY AND PATHOBIOLOGY OF ACUTE CORONARY SYNDROMES TO PHARMACOTHERAPY

The pivotal role of platelets in the pathobiology of ACS provides a strong rationale for platelet-directed pharmacotherapy as a mainstay of treatment.

Aspirin. Aspirin, a prototypic platelet antagonist developed more than a century ago, is hydrolyzed rapidly after ingestion to salicylate and acetate. Aspirin irreversibly acetylates cyclooxygenase (COX), attenuating prostaglandin metabolism and the subsequent production of thromboxane A_2 within platelets.

TABLE 20–2 Platelet P2Y12 Receptor Antagonists

P2Y12 Antagonist	Dosing	Metabolism	Pharmacokinetics	Adverse Events	Reference
Thienopyridines					
Ticlopidine	• 250 mg bid • 500-1500 mg loading dose • Orally available	• Irreversible inhibition • In vivo metabolism to active metabolite (UR-4501) • CYP enzymes 2C19, 3A4, 2D6	• $AUC_{0\text{-}12}$ 9.7 ng·h/L • C_{max} 3.1 ng/L • $T_{1/2}$ 4 h • T_{max} 2.0 h • ~65% max IPA in 8-11 days	• Hematologic adverse events including: neutropenia, thrombocytopenia, TTP or aplastic anemia • Elevated serum cholesterol and triglycerides • GI disorders, skin eruptions • Rare events: agranulocytosis, pancytopenia or leukemia • Contraindicated with cyclosporine, anticoagulants, hydantoins, or theophyllines	42-44, 126-128
Clopidogrel	• 75 mg od • 300 mg loading dose • Orally available	• Irreversible inhibition • In vivo metabolism to active form (R-130964) • CYP enzymes major: 2B6, 3A4; minor: 1A1, 1A2, and 2C19	• $AUC_{0\text{-}12}$ 100 ng·h/L • C_{max} 29 ng/L • $T_{1/2}$ 7.2-7.6 h • T_{max} 0.8-1.0 h • ~60% max IPA in 3-7 days • max IPA in ~2 hours with loading dose (PK values for inactive metabolite SR26334)	• Occasional GI disorders, skin eruptions, purpura • Rare events: cerebral hemorrhage, GI hemorrhage, liver disorders, neutropenia, taste disorders, TTP	52, 129-132
Prasugrel*	• 10-15 mg od • 40-60 mg loading dose • Orally available	• Irreversible inhibition • In vivo metabolism to active form (R-138727) • CYP enzymes 3A4, 2B6	• $AUC_{0\text{-}12}$ 122 ng·h/mL • C_{max} 80 ng/mL • $T_{1/2}$ 3.7 h • T_{max} 0.5 h • ~60% max IPA in 7-14 days • max IPA in ~1 hour with loading dose (PK values for active metabolite R-138727)	• Purpura • Major bleeding • Fatal bleeding • Minor bleeding • Headache • Dizziness	49, 52, 133-137
ATP Analogue					
Cangrelor†	• 4 $\mu g \cdot kg^{-1}\ min^{-1}$ • IV administration	• Reversible inhibition	• C_{max} 401 ng/mL • $T_{1/2}$ 2.6 min • T_{max} 15 min • clearance: 12.7 mL/min/kg • 100% max IPA ~ 15 min	• Minor bleeding • Major bleeding • Occasional GI bleeding • Potential for dyspnea	52, 131, 138-140
Cyclopentyl-triazolo-pyrimidines					
Ticagrelor	• 100-200 mg bid • Orally available	• Reversible inhibition • 1° metabolite also active (AR-C12490XX)	AZD6140: • $AUC_{0\text{-}12}$ 5530 ng·h/mL • C_{max} 810 ng/mL • T_{max} 2.82 h 1° metabolite AR-C12490XX: • $AUC_{0\text{-}12}$ 2108 ng·h/mL • C_{max} 261 ng/mL • T_{max} 3.00 h • 90-95% max IPA in 2-4 hrs (PK data for 100 mg bid steady state)	• Minor bleeding • Major bleeding • Ventricular pauses • Dizziness • Headache • Potential for dyspnea	52, 54, 94a, 141

All P2Y12 antagonists prolong bleeding time 2fold to 3fold. * Submitted for regulatory authority approval in the United States and European Union. AUC, area under the curve; CYP, cytochrome P-450; IPA, inhibitory platelet aggregation (from optical or turbidimetric platelet aggregation tests); GI, gastrointestinal; PK, pharmacokinetics.

About 80% to 90% of aspirin is absorbed through the gastrointestinal tract after oral ingestion. A much smaller proportion, 20% to 40%, is absorbed after rectal administration. Once absorbed, salicylate is detected within serum 5 to 30 minutes later, with peak concentrations attained typically within 2 hours. Enteric coating delays both absorption and time to peak concentration by 3- to 4-fold. The elimination half-life of salicylate is 15 to 20 minutes; however, COX inhibitory effects are sustained for the platelets' life-span (7 ± 2 days).

Platelet P2Y12 Receptor Antagonists

The physiologic significance of the P2Y12 interaction with ADP is borne out by the success of P2Y12 blockers in reducing the risk of cardiovascular events. Though platelet P2Y12 receptor antagonists are often considered collectively as a single drug class, differences ranging from location of receptor binding site, metabolism, biological half-life, off-target effects, reversibility, and potential drug-drug interactions are evident (Table 20-2).

Ticlopidine. Ticlopidine hydrochloride is an oral 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno-(3,2-c)-pyridine hydrochloride that, like all thienopyridines, irreversibly prevents ADP binding to the platelet P2Y12 receptor.[42] Following oral administration, ticlopidine is extensively metabolized in the liver to at least 20 different metabolites.[43] The active metabolite UR-4501 was isolated from rats administered ticlopidine, tested against human platelets in vitro, and may account for the pharmacodynamic activity of ticlopidine.[44]

Ticlopidine displays nonlinear pharmacokinetics, and drug clearance decreases substantially on repeat dosing with steady-state plasma concentrations reached 14 to 21 days after daily dosing (250 mg twice daily). Thus, doses greater

than 250 mg twice daily have minimal additional effect on platelet inhibition, but do increase the occurrence of adverse effects including neutropenia, agranulocytosis, aplastic anemia, and thrombotic thrombocytopenic purpura (TTP).[45] In healthy volunteers, ADP-induced platelet aggregation is diminished 4 days after oral drug initiation, reaching a maximal effect after 8 to 11 days.

Clopidogrel. Clopidogrel,(+)-(S)-methyl2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-yl)-acetate sulfate, is another oral thienopyridine derivative. Following oral administration, clopidogrel must be transformed in the liver to its active metabolite, which contains a free thiol group that forms a disulfide bridge with P2Y12 extracellular cysteine residues.

Pharmacokinetic data are based on the inactive metabolite of clopidogrel. This carboxylic acid derivative, representing 85% of the circulating drug-related compounds in plasma, has no effect on platelet aggregation and has a half-life of about 8 hours. The elimination half-life of the active metabolite has not been determined in vivo, but is assumed to be relatively short. Dose-dependent inhibition of ADP-induced platelet aggregation is observed 2 hours after clopidogrel administration and reaches a steady-state within 3 to 7 days with daily dosing.[46] When clopidogrel is given as a 600-mg loading dose, it achieves its mean peak antiplatelet effect 3 to 8 hours after administration.[47]

Prasugrel. The most recent thienopyridine to be clinically investigated is prasugrel, 2-acetoxy-5-(a-cyclopropylcarbonyl-2-fluoro-2-fluorobenzyl-4,5,6,7-tetrahydrothieno [3,2-c]pyridine.[48] In contrast to clopidogrel and ticlopidine, which require two-step cytochrome P-450 oxidation for generation of their active metabolites, prasugrel requires only one step, leading to a 10-fold higher plasma concentration.[49] Human carboxylesterases, found in the liver and gastrointestinal tract, efficiently mediate the conversion of prasugrel to its active metabolite, providing an explanation for the rapid achievement of maximum plasma concentrations following oral administration.[50] Prasugrel, given at doses of 10 and 20 mg once daily, achieves a robust degree of ADP-induced platelet inhibition beginning at 15 minutes, with peak response within 2 hours of administration of a 40- or 60-mg loading dose and steady-state platelet aggregation inhibition by day 3.[51]

Cangrelor. Cangrelor, N6 [-2-methylthio]-2-[3,3,3-trifluoropropylthio]-5'-adenylic acid, was developed as an intravenous, selective, and reversible P2Y12 receptor antagonist and does not require hepatic conversion to an active metabolite.[52] It is chemically similar to adenosine triphosphate (ATP) and is considered an ATP analogue. Following intravenous administration, cangrelor is metabolized primarily in the liver with a mechanism of plasma clearance determined by dephosphorylation and vascular surface (endothelial cell) endonuclease activity. Following an intravenous infusion of 4 hours' duration, plasma elimination causes a rapid decline in cangrelor concentrations, with an initial half-life of less than 5 minutes.[53]

In phase II studies of cangrelor administered at rates of 1, 2, and 4 μg/kg/minute to patients undergoing percutaneous coronary intervention (PCI), impedance-determined platelet aggregation in response to 3 μM ADP was inhibited by 94%, 87% and 99%, respectively, 15 minutes after drug administration.[53] A return toward baseline platelet aggregation occurred 15 minutes after drug cessation in the 1 and 2 μg/kg/minute dosing arms but required 30 to 60 minutes for those patients in the 4 μg/kg/minute group.

Ticagrelor. Ticagrelor, is a cyclopentyltriazolopyrimidine (CTEP), a new class of P2Y12 inhibitors. Its molecular structure is 6-[2-(3,4-difluorophenyl)cyclopropyl-1-yl]amino-2-propylthio-9ß-D-ribofuranosyl-9H-purine. It is an oral and reversible derivative of cangrelor that similarly does not require hepatic conversion to an active metabolite, although one of its metabolites (AR-C12490XX) is also pharmacologically active.

Ticagrelor and AR-C12490XX show linear dose-response relationships, with a mean time to maximal inhibition of platelet aggregation of 2 to 4 hours following 100 mg twice daily, 200 mg twice daily, and 400 mg once daily dosing. On average, the degree of platelet inhibition in response to 20 μM ADP is 80% to 90% with the highest doses.[54]

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

The $\alpha_{IIb}/ß_3$ receptor belongs to the integrin family of adhesion receptors that are found predominantly on the surface of platelets and megakaryocytes. This receptor is found in large numbers (80,000 copies per platelet) and consists structurally of a non-covalently linked heterodimer. GP IIb/IIIa receptor antagonists occupy the α_{IIb}/β_3 receptor, inhibiting fibrinogen-mediated platelet aggregation. There are currently three intravenous platelet GP IIb/IIIa receptor antagonists that are used in clinical practice (Table 20-3).

Abciximab. Abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody c7E3.

After an intravenous bolus, free plasma concentrations of abciximab decrease rapidly with an initial half-life of less than 10 minutes and a second-phase half-life of 30 minutes, representing rapid binding to the platelet GP IIb/IIIa receptor. Abciximab remains in the circulation for 10 or more days in the platelet-bound state.

Pharmacodynamics. Intravenous administration of abciximab in doses ranging from 0.15 mg/kg to 0.3 mg/kg produces a rapid dose-dependent inhibition of platelet aggregation in response to ADP. At the highest dose, 80% of platelet GP IIb/IIIa receptors are occupied within 2 hours, and platelet aggregation, even with 20 μM of ADP, is completely inhibited. Sustained inhibition is achieved with prolonged infusions (12 to 24 hours), and low-level receptor blockade is present for 10 days after cessation of the infusion; however, platelet inhibition during infusions beyond 24 hours has not been well characterized. Platelet aggregation in response to 5 μM ADP returns to greater than or equal to 50% of baseline within 24 hours in most cases (Fig. 20-5).[55]

Tirofiban. Tirofiban, a synthetic 495-kd nonpeptide tyrosine derivative, is a selective competitive antagonist of the platelet GP IIb/IIIa receptor.

The pharmacokinetics of tirofiban are linear, and plasma concentrations are proportional to dose after intravenous infusions of 0.05 to 0.4 mg/kg/minute for 1 hour or 0.1 to 0.2 mg/kg/minute for 4 hours in healthy individuals. Concomitant administration of aspirin or clopidogrel does not affect pharmacokinetics.

Tirofiban is approximately 65% bound to plasma proteins, and binding is independent of drug concentrations over a wide range. The steady-state volume of distribution ranges from 22 to 42 L.

After intravenous administration, plasma concentrations of tirofiban decline in a biphasic manner. The half-life averages 1.5 to 2 hours. Clearance is predominantly (65% to 70%) through renal excretion, and metabolism of the drug is limited. Plasma clearance of tirofiban is 20% to 25% lower in older patients (≥65 years old) and can be reduced by 50% or more in patients with marked renal insufficiency (creatinine clearance <30 mL/minute). Drug clearance is not influenced by gender, race, or mild-to-moderate hepatic insufficiency. Tirofiban is removed to a variable degree by hemodialysis.

Pharmacodynamics. Tirofiban mimics the geometric stereotactic and conformational characteristics of the α_{IIb}/β_3 receptor arginine-glycine-aspartic acid (RGD) sequence,

TABLE 20–3 Individual Characteristics and Dosing of Glycoprotein IIb/IIIa Receptor Antagonists

Characteristics	Abciximab	Eptifibatide	Tirofiban
Type	Antibody	Peptide	Nonpeptide
Molecular weight (d)	~50,000	~800	~500
Platelet-bound half-life	Long (hr)	Short (sec)	Short (sec)
Plasma half-life	Short (min)	Extended (2 hr)	Extended (2 hr)
Drug-to-GP IIb/IIIa receptor ratio	1.5-2.0	250-2500	>250
50% return of platelet function (without transfusion)	12 hr	~4 hr	~4 h
Antagonist dosing			
PCI			
Bolus	0.25 mg/kg	Double bolus 180 µg/kg/min(10 min apart)	10 µg/kg
Infusion	0.125 µg/kg/min for 12 hr	2 µg/kg/min for 20-24 hr	0.5 µg/kg/min
ACS			
Bolus	Not recommended*	180 µg/kg over 30 min	0.4 µg/kg over 30 min
Infusion		2 µg/kg/min up to 72 hr	0.1 µg/kg/min for 48-108 hr
Renal dysfunction			
Creatinine clearance ≥50 mL/min	No adjustment required	180 µg/kg over 30 min; 0.5 µg/kg/min infusion	0.2 µg/kg over 30 min
Creatinine clearance <50 mL/min	Adjustment required‡	Contraindicated	0.5 µg/kg/min infusion†

*Use of abciximab for ACS in absence of planned PCI not recommended.
†Dose of tirofiban for patients with creatinine clearance < 30 mL/min. Experience limited.
‡Contraindicated in patients requiring renal dialysis.
From Becker RC, Armani AM: Antiplatelet therapy: In Theroux P (ed): Acute Coronary Syndromes: A Companion to Braunwald's Heart Disease. Philadelphia, Saunders, 2003.

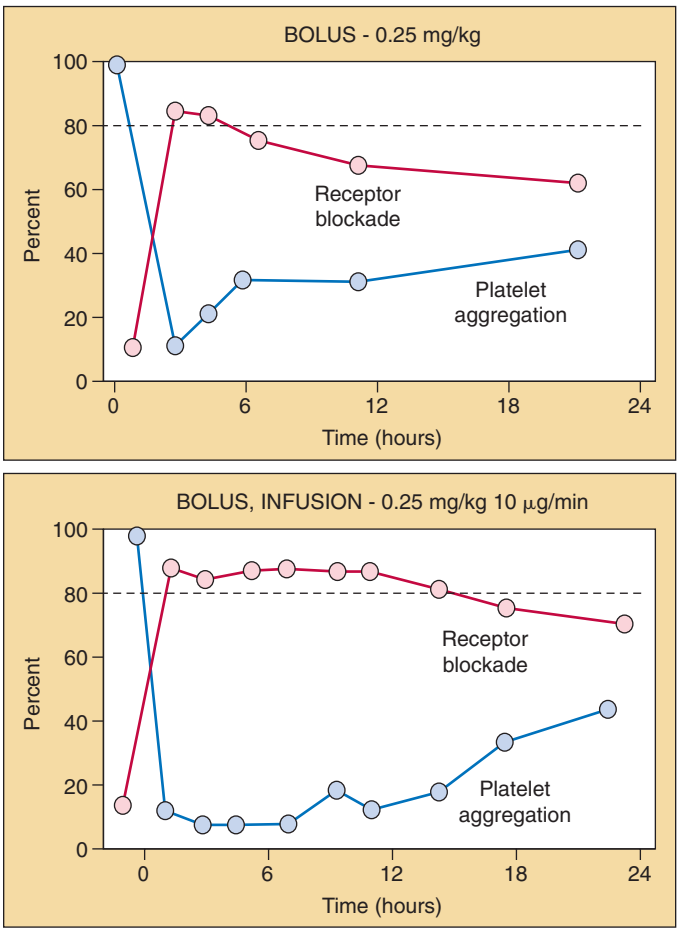

FIGURE 20–5 Duration of GP IIb/IIIa receptor blockade and associated inhibition of platelet aggregation following a bolus and infusion of abciximab. *(From Uprichard A: Handbook of Experimental Pharmacology. Berlin, Springer Verlag, 1995, pp 175-208.)*

interfering with fibrinogen surface binding and platelet aggregation.

Three doses of tirofiban were studied in phase I clinical trials: bolus dose of 5, 10, or 15 µg/kg followed by a continuous intravenous infusion of 0.05, 0.10, or 0.15 µg/kg/minute. A dose-dependent inhibition of ex vivo platelet aggregation was observed within several minutes of bolus administration with sustained inhibition during the maintenance infusion.[56] For patients with NSTE ACS the following dosing strategy is recommended: loading dose for 30 minutes—0.4 µg/kg/min followed by a maintenance infusion of 0.1 µg/kg/min.

Plasma clearance of tirofiban is decreased substantially in patients with severe renal impairment (creatinine clearance <30 mL/minute), including patients requiring hemodialysis. These patients should receive half the usual infusion rate.

Eptifibatide. Eptifibatide, a synthetic cyclic heptapeptide, is a selective competitive antagonist of the platelet GP IIb/IIIa receptor.

The pharmacokinetics of eptifibatide are linear, and plasma concentrations are proportional to dose after intravenous administration of 90 to 250 µg/kg and infusions of 0.5 to 3 mg/kg/minute. Concomitant administration of aspirin or heparin does not influence the pharmacokinetics of eptifibatide.[57] Dosing strategies, to include high-dose single bolus administration, have been investigated among patients with ACS.[58-60]

Eptifibatide is approximately 25% bound to plasma proteins, principally albumin. The volume of distribution ranges from 185 to 260 mL/kg.

Plasma concentrations of eptifibatide decline in a biexponential manner after intravenous administration. The half-life ranges from 2.5 to 2.8 hours. Eptifibatide is eliminated by renal and nonrenal mechanisms. The drug undergoes deamination within plasma to a metabolite that is responsible for approximately 40% of the platelet inhibitory effects. Clearance of eptifibatide is proportional to body weight and creatinine clearance and inversely proportional to age. Renal clearance is responsible for 40% to 50% of total body clearance. Eptifibatide is removed to a variable degree by hemodialysis.

Pharmacodynamics. Early studies of patients undergoing PCI determined that bolus doses of 135 μg/kg or higher yielded greater than 80% inhibition of ADP-mediated platelet aggregation in most (75%) patients. A double bolus strategy (180 μg/kg, administered twice, 10 minutes apart) achieved maximal inhibition in a greater proportion of patients.[61] Platelet aggregation returns to 50% of baseline 4 hours after infusion termination.

Dose adjustments have not been recommended with mild renal impairment (serum creatinine <2 mg/dL). Appropriate dosing of eptifibatide is based on creatinine clearance, a more accurate estimate of renal function than serum creatinine alone. Patients with a creatinine clearance of <50 mL/min should receive an infusion of 1 μg/kg/min representing a 50% reduction of the normal infusion. Eptifibatide should not be used in patients with dependence on renal dialysis.

PLATELET-DIRECTED PHARMACOTHERAPY

Clinical Trials, Evidence, and Administration Strategies in Acute Coronary Syndromes

The contemporary management of patients with ACS has been summarized in recently published guidelines crafted by the American College of Cardiology, American Heart Association, and European Society of Cardiology[62,63] and by the American College of Chest Physicians.[64]

Short-term Administration

Aspirin. International Studies of Infarct Survival (ISIS-2) was a randomized, placebo-controlled, blinded trial of short-term therapy with IV streptokinase (SK), oral aspirin (160 mg/d for 1 month), both or neither, among 17,187 patients with suspected myocardial infarction (MI). In addition to a 23% relative risk reduction (RRR) in 5-week vascular mortality among patients receiving SK, there was a 21% reduction among those receiving aspirin and a 40% reduction among those receiving a combination of SK and aspirin, which are all highly significant reductions. The early reduction in mortality with aspirin persisted when the patients were observed for a mean of 15 months. Aspirin reduced the risk of nonfatal reinfarction by 49% and nonfatal stroke by 46%. The increased rate of early nonfatal reinfarction noted when SK therapy was used alone is consistent with marked platelet activation after fibrinolytic therapy and was completely resolved when aspirin was added (3.8% vs. 1.3%; $P < .001$).

Aspirin added to the benefit of SK therapy in all groups examined. In particular, among patients younger than 70 years of age, the combination markedly reduced mortality from 23.8% to 15.8% ($P < .001$) without increasing hemorrhage or stroke. Because of the overall poor prognosis among older individuals with acute MI, the absolute number of lives saved with aspirin and thrombolytic therapy increases with age (i.e., 2.5 per 100 treated patients <60 years of age and 7 to 8 per 100 treated patients 60 years of age).[65]

ISIS-2 showed that short-term aspirin therapy for MI decreases mortality and reinfarction, has benefits in addition to those of fibrinolysis, and reduces reinfarction after fibrinolytic therapy. Consequently, aspirin therapy for patients with acute MI should accompany fibrinolytic therapy. Although associated with an increased rate of minor bleeding from 1.9% to 2.5%, aspirin therapy was not associated with an increased risk of major bleeding, including hemorrhagic stroke. The benefit of aspirin, in contrast to that of SK, was independent of the time of onset of treatment. However, early administration seems prudent.[66]

P2Y12 Receptor Antagonists. The CLARITY, TIMI, 28[64,67] and COMMIT[68] trials evaluated the addition of clopidogrel to antithrombotic therapy with aspirin, heparin, and a fibrinolytic agent. In the CLARITY trial, the addition of a loading dose of 300 mg of clopidogrel followed by 75 mg/day in 3491 patients younger than 75 years of age with acute ST-segment elevated myocardial infarction (STEMI) was associated with a significant 36% reduction in the composite primary end point of death, MI, or an occluded infarct-related coronary artery (95% confidence interval [CI]; 27%-47%; $P < .001$) at the time of angiography. The greatest effect of clopidogrel was on coronary occlusion; this trial did not demonstrate benefits on reducing either death or MI. The benefit did not come at the expense of increased bleeding despite the concomitant use of a fibrinolytic agent, aspirin, unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH). In addition, the PCI-CLARITY subset of the trial demonstrated significantly better outcomes in the 1863 patients who underwent angioplasty after clopidogrel therapy.

The Chinese COMMIT trial[4] of 45,852 patients with acute MI, half of whom received reperfusion therapy, demonstrated benefit from clopidogrel 75 mg/day compared with placebo; both groups received aspirin. The primary end point of death, MI, or stroke was reduced by 9% (10.1% vs. 9.3%, $P = .002$); mortality was reduced by 7% (8.1% vs. 7.5%, $P = .03$). Overall, when all transfused, fatal, or cerebral bleeds were considered together, there was no significant excess risk associated with the use of clopidogrel (134 [0.58%] clopidogrel vs. 125 [0.55%] placebo; $P = .59$). The average duration of treatment with clopidogrel for CLARITY and COMMIT was 16 days and 14 days, respectively.[67]

Long-Term Administration

Aspirin. The Antiplatelet Trialists' Collaboration[68] update included 287 studies involving 135,640 high-risk (acute or previous vascular disease or another predisposing condition) patients in comparisons of antiplatelet therapy versus control and 77,000 similar patients in comparisons of different antiplatelet regimens. The analysis extended the direct evidence of benefit from platelet-directed therapy, predominantly with aspirin, to a much wider range of patients at high risk including those with ACS.[68]

Overall, 7705 (10.7%) serious vascular events occurred in 71,912 high-risk patients allocated antiplatelet versus an adjusted total of 9502 (13.2%) such events among 72,139 control patients (22% odds reduction; $P = .0001$). Antiplatelet therapy was associated with a highly significant 15% relative reduction in vascular deaths ($P = .0001$) (similar across high- and low-risk groups), all-cause mortality ($P < .0001$), nonfatal MI (34% odds reduction; $P < .001$), nonfatal MI or death from coronary heart disease (26% odds reduction; $P < 0.001$), and stroke (25% odds reduction; $P < .001$). Overall, the relative odds of experiencing a major extracranial hemorrhage was increased 60% with antiplatelet therapy (odds ratio, 1.6; $P < .001$). The increase in fatal hemorrhage was not significantly different from that for nonfatal hemorrhage, although only the excess of nonfatal hemorrhagic events achieved statistical significance.

The optimal dose of aspirin for the prevention of cardiovascular events has not been definitively established by directly comparing two different dosages in large clinical trials. The updated meta-analysis does, however, provide useful information on the effects of different doses of aspirin. Overall, among 3570 patients in three trials directly comparing aspirin doses (75 mg vs. <75 mg/day), there were significant differences in vascular events (two trials compared 75 to 325 mg/day aspirin vs. <75 mg/day and one trial compared 500 to 1500 mg of aspirin daily vs. <75 mg/day) favoring lower doses. Considering both direct and indirect comparisons of aspirin dose, vascular events were reduced 19% with 500 to 1500 mg/day, 26% with 160 to 325 mg/day, and 32% with 75 to 150 mg/day. These data provide indirect support

for administration of an aspirin dose of 75 to 100 mg/day for cardiovascular disease treatment.[69]

The benefit derived from antiplatelet therapy in patients with coronary artery disease (CAD), unstable angina (UA), acute MI, and previous MI is well established; additionally, the added benefit from multitargeted antiplatelet regimens, particularly among high-risk patients with non–ST-elevation myocardial infarction (NSTEMI) ACS, is now clearly established.

P2Y12 Receptor Antagonists. In the CURE trial,[70] 12,562 patients with NSTEMI ACS were randomly assigned to receive clopidogrel (300 mg immediately followed by 75 mg/day) or placebo in addition to aspirin (75 to 325 mg/day) for 3 to 12 months. The first primary outcome, a composite of death from cardiovascular causes, nonfatal MI or stroke, occurred in 9.3% and 11.4% of patients given clopidogrel and placebo, respectively (relative risk [RR] 0.80; 95% CI, 0.72 to 0.90; $P < .001$). The compelling benefit in CURE is in reducing nonfatal MI (5.2% vs. 6.7%; RR, 0.77; 95% CI, 0.67 to 0.89); modest trends primarily (nonsignificant) suggested the possibility of small reductions in death (5.1% vs. 5.5%; RR, 0.93; 95% CI, 0.79 to 1.08), and stroke (1.2% vs.1.4%; RR 0.86; 95% CI, 0.63 to 1.18) with clopidogrel.

Significantly fewer patients in the clopidogrel group experienced recurrent angina (20.9% vs. 22.9%; RR, 0.91; 95% CI, 0.85 to 0.98; $P = .01$). The benefits of clopidogrel were consistent across a broad range of patient subsets including those with MI, ST-segment deviation, elevated cardiac biomarkers, diabetes mellitus, age older than 65 years, and high-risk features. Although the use of concomitant GP IIb/IIIa inhibitors was low in CURE, the treatment effect of clopidogrel was consistent among those receiving and not receiving the intravenous platelet inhibitors.

Major bleeding (defined as disabling hemorrhage, intraocular hemorrhage leading to visual loss, or bleeding requiring transfusion of at least 2 units of blood) was significantly more common in clopidogrel-treated patients (3.7% vs. 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; $P = .001$). Life-threatening bleeding (fatal hemorrhage or causing a reduction in hemoglobin of 5 g/dL or substantial hypotension requiring inotropic support, surgical intervention; symptomatic intracranial hemorrhage, or transfusing of 4 units of blood) was also more common, although the difference did not reach conventional levels of statistical significance (2.2% vs. 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56). There was not an excess rate of fatal bleeding, bleeding that required surgical intervention, or hemorrhagic stroke. The number of patients requiring transfusion of 2 units of blood was higher in the clopidogrel group (2.8% vs. 2.2%; $P = .02$).

Compared with aspirin alone, there was an excess of minor and major bleeding with the combination of aspirin and clopidogrel in patients with NSTEMI in the CURE trial,[71] although the incidence of life-threatening bleeding was not different between the two groups.[72] Using the TIMI criteria for major bleeding, the rate of major bleeding with the combination of aspirin plus clopidogrel was similar to that with aspirin alone (1.1% and 1.2%, respectively; $P = .70$). Major or life-threatening bleeding in the PCI-CURE study was similar in the two groups, even in patients who received a GP IIb-IIIa inhibitor.

The rate of major bleeding with clopidogrel was higher early (within 30 days of randomization; 2.0% vs. 1.5%; RR, 1.31; 95% CI, 1.01 to 1.70) and also late (>30 days after randomization: 1.7% vs. 1.1%; RR, 1.48; 95% CI, 1.10 to 1.99). Bleeding associated with coronary artery bypass grafting (CABG) was particularly high among patients receiving clopidogrel within 5 days of surgery (9.6% vs. 6.3%; $P = .06$) but bleeding was not different between the groups when clopidogrel had been discontinued for more than 5 days. Overall, the risk of minor bleeding was significantly higher in patients treated with clopidogrel (5.1% vs. 2.4%; $P = .001$).

The two most recently developed and studied P2Y12 receptor antagonists, prasugrel and ticagrelor will be discussed later in the section "Emerging Platelet-Directed Pharmacotherapy."

Dose of Aspirin with Combination Platelet-Directed Therapy. Long-term aspirin therapy is recommended for patients with CAD who undergo any revascularization procedure, including PCI. When aspirin is given in combination with other antiplatelet agents or with anticoagulants, it is reasonable to use a daily dose of 75 to 100 mg, rather than 325 mg, to minimize hemorrhagic risk.

The CURRENT-OASIS 7 trial[123] randomized more than 25,000 patients with ACS to either low-dose aspirin (75-100 mg daily) or high-dose aspirin (300-325 mg daily for the first 7 days) and, in a separate randomization to either standard-dose lopidogrel (300 mg loading dose, followed by 75 mg daily on days 2-30) or high-dose clopidogrel (600 mg loading dose, followed by 150 mg daily on days 2-7). The primary outcome was the composite of death from cardiovascular causes, MI, or stroke at 30 days. In the overall cohort, which included 7855 patients who did not undergo PCI or in whom therapy was discontinued in anticipation of coronary artery bypass grafting, there was no significant difference in the primary outcome for high dose aspirin or high dose clopidogrel. Among the 17,232 patients who underwent PCI, high dose clopidogrel was associated with a significant reduction (15%) in the composite endpoint, driven in large part by a 22% reduction in the risk of MI. There was also a 42% reduction in the risk of definite start thrombosis. Severe bleeding and transfusions were increased by approximatedly 40% with high-dose clopidogrel compared to standard dosing. The overall benefit beyond 30 days is unknown (European Society of Cardiology, Barcelon, Spain, 2009).

A dose of 75 to 100 mg/day is supported by a post hoc analysis of data derived from the CURE study.[70] Patients were classified into three aspirin-dose groups: less than 100 mg, 101 to 199 mg, and 200 mg.[74] The combined incidence of cardiovascular death, MI, or stroke was reduced by clopidogrel regardless of aspirin dose, but the incidence of major bleeding increased with higher doses, both in patients randomized to aspirin plus placebo (1.9%, 2.8%, and 3.7%, respectively; $P = .0001$) and in those given aspirin plus clopidogrel (3.0%, 3.4%, and 4.9%, respectively; $P = .0009$).

Platelet-Directed Therapy Following Percutaneous Coronary Intervention. Extended treatment with the combination of aspirin and clopidogrel after PCI for an ACS[73] or after elective angioplasty[72] reduces the rate of ischemic events. The CREDO trial[72] was a randomized, blinded, placebo-controlled trial conducted in 2116 patients undergoing elective PCI. Patients were randomly assigned to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 hours before PCI. Thereafter, all patients received clopidogrel (75 mg/day) until day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel (75 mg/day), while those in the control group received placebo. Both groups received aspirin throughout the study. The 12-month incidence of the composite of death, MI, or stroke in the intention-to-treat population was reduced by 26.9% in patients treated with long-term clopidogrel therapy ($P = .02$). Drug-eluting stents (DES) were not yet available and therefore were not included in the study.

In the CREDO trial, major bleeding as defined by the TIMI criteria tended to be higher in the clopidogrel group than in those given placebo (8.8% and 6.7%, respectively; $P = .07$), although most of the major bleeding episodes were related to invasive procedure, such as CABG. Minor bleeding episodes were significantly more common with combination antiplatelet therapy in both the CURE and PCI-CURE studies. The CREDO trial did not find differences in minor bleeding between the two groups.

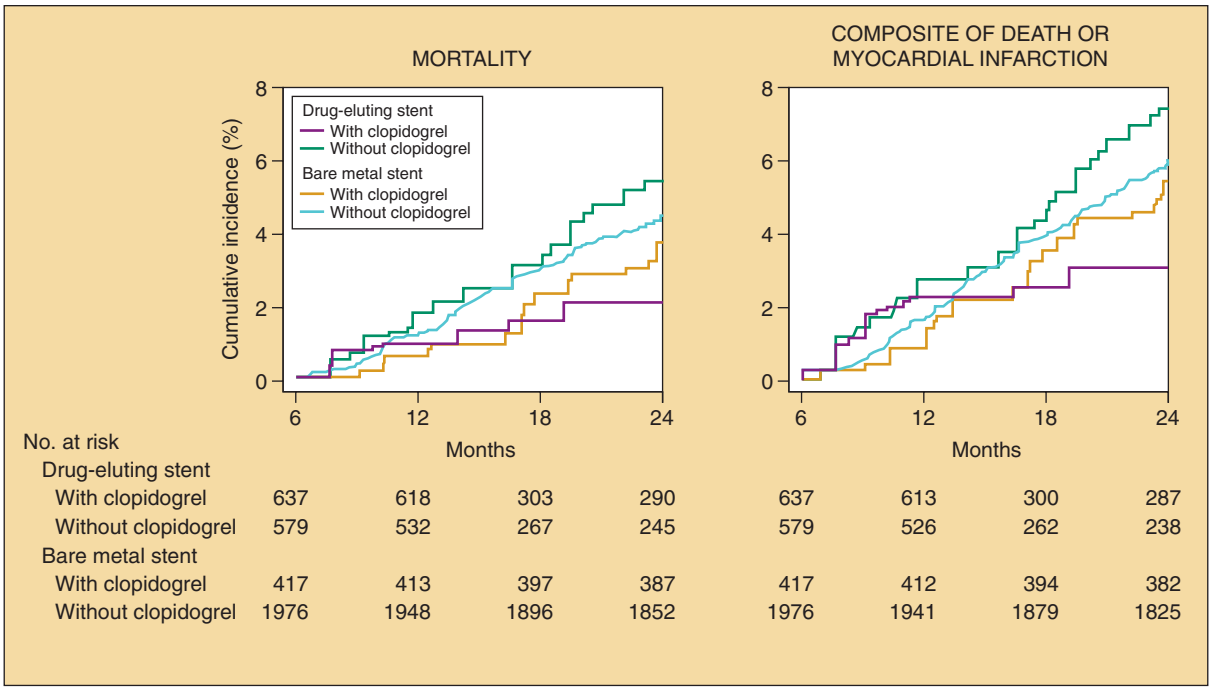

FIGURE 20–6 Adjusted cumulative mortality rates and cumulative rates of composite of death or myocardial infarction using the 6-month landmark analysis. *(From Eisenstein EL, Anstrom KJ, Kong DF, et al: Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159-168.)*

Stent Thrombosis Following Percutaneous Coronary Intervention. Although uncommon, stent thrombosis represents a severe complication of stent implantation with a high rate of morbidity (mostly MI) and mortality.[75] Stent thrombosis can occur hours after placement (acute stent thrombosis), days thereafter (subacute stent thrombosis), or beyond 30 days (late stent thrombosis).[76] Reports on the predictors of stent thrombosis following DES implantation have found that clinical (diabetes and renal failure), angiographic (bifurcation disease), and care (premature termination of antiplatelet therapy) characteristics are all associated with a higher risk of stent thrombosis. Impaired or delayed endothelialization, particularly with placement in the setting of an ACS, may also affect thrombosis occurrence.

Bare metal stent (BMS) thrombosis, with the introduction of combined therapy with aspirin and clopidogrel, occurs infrequently with most estimates being at less than 1% of patients, and is unusual after the first month.[77] In contrast, stent thrombosis following DES, although less frequent with dual antiplatelet therapy, can occur months to years after implantation. In the PREMIER Registry,[78] 500 DES-treated MI patients discharged from the hospital on aspirin and thienopyridine therapy were followed for 11 months. A total of 68 patients (13.6%) discontinued thienopyridine drugs within 30 days of hospital discharge, and on follow-up were more likely to die during the next 11 months (7.5% vs. 0.7%; adjusted hazard ratio, 9.0; 95% CI, 0.2 to 60.5; $P < .0001$) and to be rehospitalized (23% vs. 14%; adjusted hazard ratio, 1.5; 95% CI, 0.78 to 3.0; $P = .08$).

An observational study from the Duke Cardiovascular Database[79] including 3165 patients receiving BMS and 1501 patients with DES who were event free (death, MI, revascularization) at 6 months and 12 months, were followed up and self-reported clopidogrel use was used to classify patients into four groups: BMS with clopidogrel, BMS without clopidogrel, DES with clopidogrel, and DES without clopidogrel. Among patients with BMS, clopidogrel did not influence the incidence of death or MI at 24 months; however, in patients with DES, continued use of clopidogrel was associated with lower rates of death (0% vs. 3.5%; 95% CI, 5.9 to 1.1%; $P = .004$) and death or MI (0.0% vs. 4.5%; 95% CI, 7.1 to 1.9; $P < .001$) (Fig. 20-6, *left* and *right panels*).

Information regarding the optimal duration of long-term aspirin and clopidogrel following DES continues to evolve. An American Heart Association Science Advisory stressed the importance of at least 12 months of uninterrupted dual antiplatelet therapy and the education of patients and providers about the potential hazards associated with premature discontinuation of these drugs.[80] The optimal duration of dual platelet-directed therapy and the preferred strategy for clopidogrel discontinuation (abrupt vs. tapered) is being addressed in ISAR-SAFE and ISAR-REBOUND/ISAR-CAUTION, respectively.

Triple Antithrombotic Therapy. Treatment of patients with coronary stents becomes a challenge when they also require treatment with vitamin K antagonists (VKA) because of associated atrial fibrillation, mechanical heart valve replacement, and other indications for long-term VKA therapy. Stent thrombosis is more likely when clopidogrel is withheld, whereas it is likely that stroke risk (in atrial fibrillation and mechanical valve patients) increases if VKA is withdrawn after stenting. However, bleeding risk increases when VKA is added to aspirin or clopidogrel or to both.

The CRUSADE Registry illustrates current practice patterns for combined antithrombotic therapy.[81] The study population comprised 103,742 patients enrolled between May 2003 and June 2006. A total of 7201 patients (7% of the total population) were receiving VKA therapy at the time of hospital admission for ACS. From a population of 5673 patients with complete outcomes and medication data, 1357 (24%) were not discharged on a VKA. Patients in whom VKA therapy was discontinued more often experienced major bleeding and required a blood transfusion during their hospitalization and were more likely to have undergone PCI with stenting than those who continued VKA therapy. Overall, aspirin, clopidogrel, and VKA were used together in 59% of patients.

Multivariable regression analysis demonstrated the following factors independently associated with a decision not to continue VKA at the time of hospital discharge: discharge clopidogrel (odds ratio [OR] 3.11; 95% CI, 2.44 to 3.95), red blood cell transfusion (OR, 1.72; 95% CI, 1.18 to 2.52), nonwhite race (OR, 1.47; 95% CI, 1.15 to 1.89), prior stroke (OR, 1.22; 95% CI, 1.01 to 1.49) and PCI with or without stenting (OR, 1.04; 95% CI, 0.83 to 1.30). Stroke risk, as estimated by the $CHADS_2$ score, was not associated with discharge VKA therapy. In contrast, when stratified by hemorrhagic risk that included age 65 years, prior stroke, history of bleeding, hematocrit of less than 30%, diabetes mellitus, and a serum creatinine greater than 1.5 mg/dL, patients with a higher risk score were less likely to receive VKA at the time of discharge. Thus, the CRUSADE Registry experience suggests that a perceived risk of hemorrhage may influence a clinician's decision to continue VKA to a greater degree than the perceived risk for thrombosis.

In the GRACE Registry,[82] 800 patients with an ACS who underwent PCI and stenting (130 patients received a DES) were discharged on VKA and either dual (n = 580) or single (n = 220) antiplatelet therapy: data on the type of stent (BMS vs. DES) were available on 482 patients. Approximately 22% of patients with a DES were discharged on a VKA and single antiplatelet agent. Use of single antiplatelet therapy was more common in Europe than in the United States (34% vs. 17%; $P < .001$). There were no differences in major bleeding during hospitalization or in the combined 6-month outcome of death or MI. At 6 months, one fourth to one third of patients were not receiving antiplatelet therapy, only a VKA. Among patients treated initially with single antiplatelet therapy, the use of either aspirin or thienopyridine in combination with VKA was associated with similar outcomes. An analysis of 66 patients discharged from the Mayo Clinic after PCI with stenting who also had a concomitant indication for VKA therapy reported that six patients (9.2%) required medical attention after major hemorrhage.[83]

A population-based observational cohort study[84] included a total of 21,443 elderly survivors of acute MI. Hospitalizations for bleeding were observed in 1428 patients (7%). Rates of bleeding, compared with aspirin alone, were higher, by approximately twofold, with combined antiplatelet, VKA-antiplatelet, and three-drug combination therapy; however, the overall risk when considered on a per patient-year basis was low.

A retrospective analysis using computerized PCI databases in six western Finnish hospitals[85] identified 239 patients with a long-term indication for VKA therapy. A similar number of patients undergoing PCI who did not have an indication for VKA served as the control group. Warfarin treatment was an independent predictor of death, MI, target vessel revascularization, and stent thrombosis (composite outcome measure) at 12-month follow-up (OR, 1.7; 95% CI, 1.0 to 3.0; $P = .05$), and its use was also associated with major hemorrhage (OR, 3.4; 95% CI, 1.2 to 9.3; $P = .02$). Triple therapy was employed in 48% of patients receiving stents. Stent thrombosis was highest in patients treated with VKA and aspirin. The incidence of stroke was highest (8.8%) among patients in whom VKA was substituted with double antiplatelet therapy. The case-control study suggests that stent thrombosis is more likely when clopidogrel is withheld, and stroke risk increases when VKA is withdrawn after stenting. Bleeding can occur with either VKA plus aspirin or clopidogrel or triple therapy.

In the absence of randomized, controlled clinical trials, when VKA therapy is clearly indicated (as in a patient with atrial fibrillation and a history of prior stroke), frequent international normalize ratio (INR) monitoring, if possible through an experienced anticoagulation clinic, should be undertaken, with consideration for targeting the lower end of the therapeutic range. Similarly, the lowest effective aspirin dose should be employed with combination therapies. Clinicians should consider proton pump inhibitors, particularly among patients with risk factors or a prior history of gastritis. peptic ulcer disease, or both. The role of concomitant vitamin K supplementation to achieve greater INR stability and, in turn, reduce hemorrhagic risk requires further investigation.

Among patients undergoing PCI with strong consideration of concomitant stent placement, a BMS should be considered to minimize the duration of triple therapy—typically 4 weeks, followed by VKA plus aspirin.[86] While this is a shorter duration of aspirin and clopidogrel than is indicated typically based on all available data (12 months), 4 weeks represents the minimum length of dual antiplatelet therapy that seems associated with the period of risk from stent thrombosis. Whenever possible, clinicians should avoid quadruple antithrombotic therapy (LMWH, VKA, aspirin, thienopyridine) unless the patient is at very high risk for thrombosis (and at very low risk for bleeding).

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

A systematic overview, using patient-level data, by Boersma and coworkers[87] included all 31,402 patients presenting with NSTE ACS enrolled in trials of GP IIb/IIIa inhibitors randomizing 1000 patients. Overall there was a significant 1.2% absolute decrease in the incidence of death or MI at 5 days (5.7% vs. 6.9%), a highly significant 16% relative reduction in the odds of death or MI (OR, 0.84; 95% CI, 0.77 to 0.93, $P = .0003$) (Fig. 20-7). Boersma and associates, in a meta-analysis of three trials[88] (CAPTURE,[89] PRISM-PLUS,[90] PURSUIT),[91] also demonstrated a convincing effect of the GP IIb/IIIa inhibitors on outcome in patients before they underwent coronary procedures, after they underwent coronary procedures, or in individuals who did not receive coronary procedures. More recently the ACUITY trial[92] investigators tested a strategy of upstream versus delayed (reserved for PCI) GP IIb/IIIa inhibitor administration.

While there was less major bleeding associated with the delayed usage (4.9% vs. 6.1%; $P = .009$), this strategy was not shown to be noninferior to an upstream usage strategy with regard to the ischemic composite of 30-day death, MI, or unplanned revascularization for ischemia (7.9% vs. 7.1%; RR, 1.12; 95% CI, 0.97 to 1.29; $P = .044$). The EARLY-ACS study[93] compared a strategy of early routine administration of eptifibatide with delayed provisional administration in 9492 patients with NSTE-ACS assigned to an invasive strategy. The primary composite endpoint of death, MI, recurrent ischemia requiring urgent revascularization, or occurrence of a thrombotic complication during PCI that required "bailout" eptifibatide therapy at 96 hours was observed in 9.3% of patients in the early eptifibatide group and 10% in the delayed group (OR, 0.92; 95% CI, 0.80 to 1.06; $P = .23$). At 30 days, the rate of death or MI was 11.2% and 12.3%, respectively (OR, 0.89; 95% CI, 0.79 to 1.01; $P = .08$). Early eptifibatide administration was associated with higher rates of bleeding and red cell transfusion.

Emerging Platelet-Directed Pharmacotherapy

The development of platelet-directed pharmacotherapy with optimized properties to include more potent platelet inhibition, as well as rapid-onset and rapid-offset pharmacodynamics is proceeding rapidly. One or more agents are poised to enter the arena of patient care in the near future.

Prasugrel, a third-generation thienopyridine-based P2Y12 receptor antagonist, was compared with clopidogrel in a study of 13,608 moderate-to-high-risk patients with ACS scheduled to undergo PCI.[94] The primary efficacy endpoint of death from cardiovascular causes, nonfatal MI or nonfatal

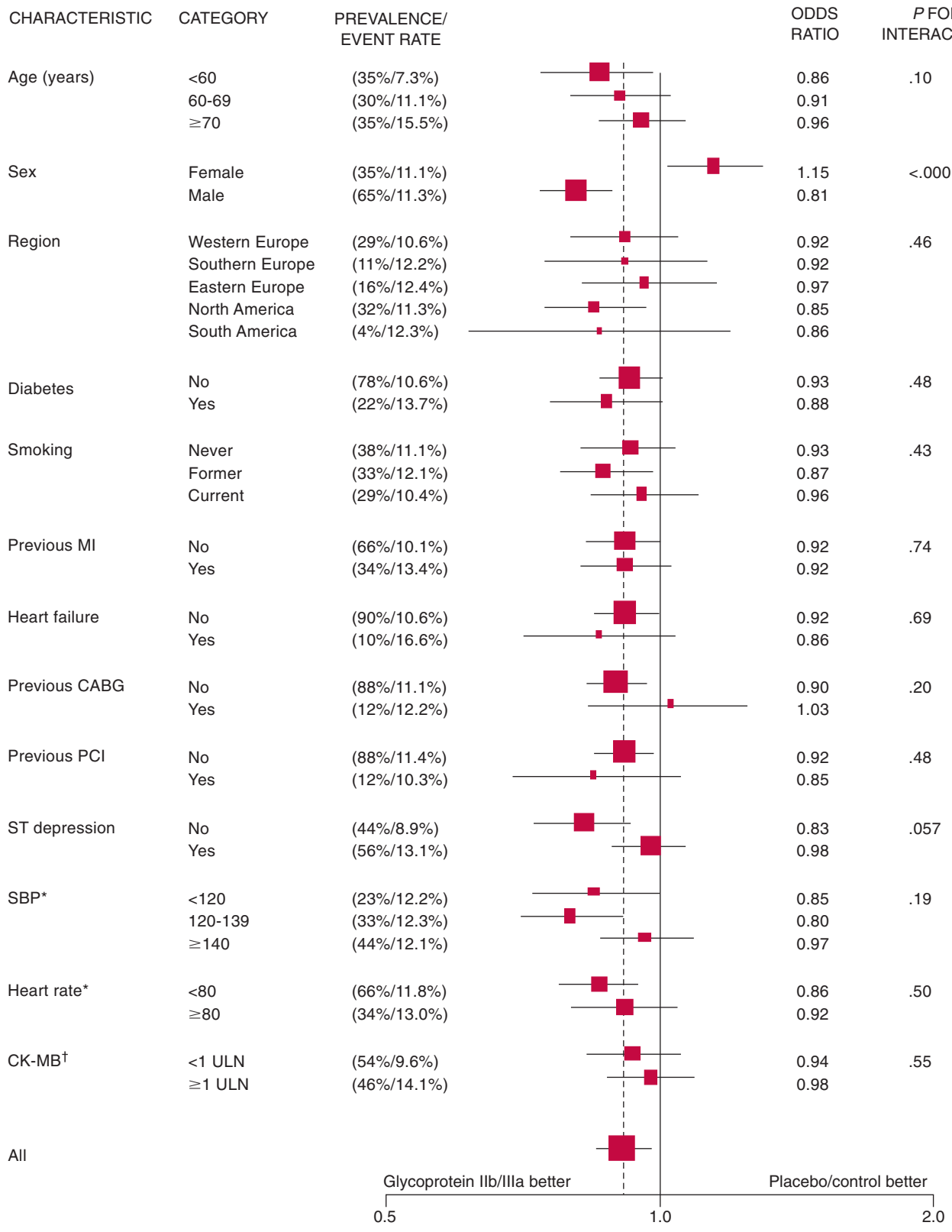

FIGURE 20–7 Systematic overview of clinical trials including patients with ACS receiving platelet GPIIb/IIIa receptor antagonists. There is consistency of benefit across multiple patient and clinical subsets. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; CK-MB, relative kinase-myocardial band. *(From Harrington RA, Becker RC, Cannon CP, et al: Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2008;133:670S-707S.)*

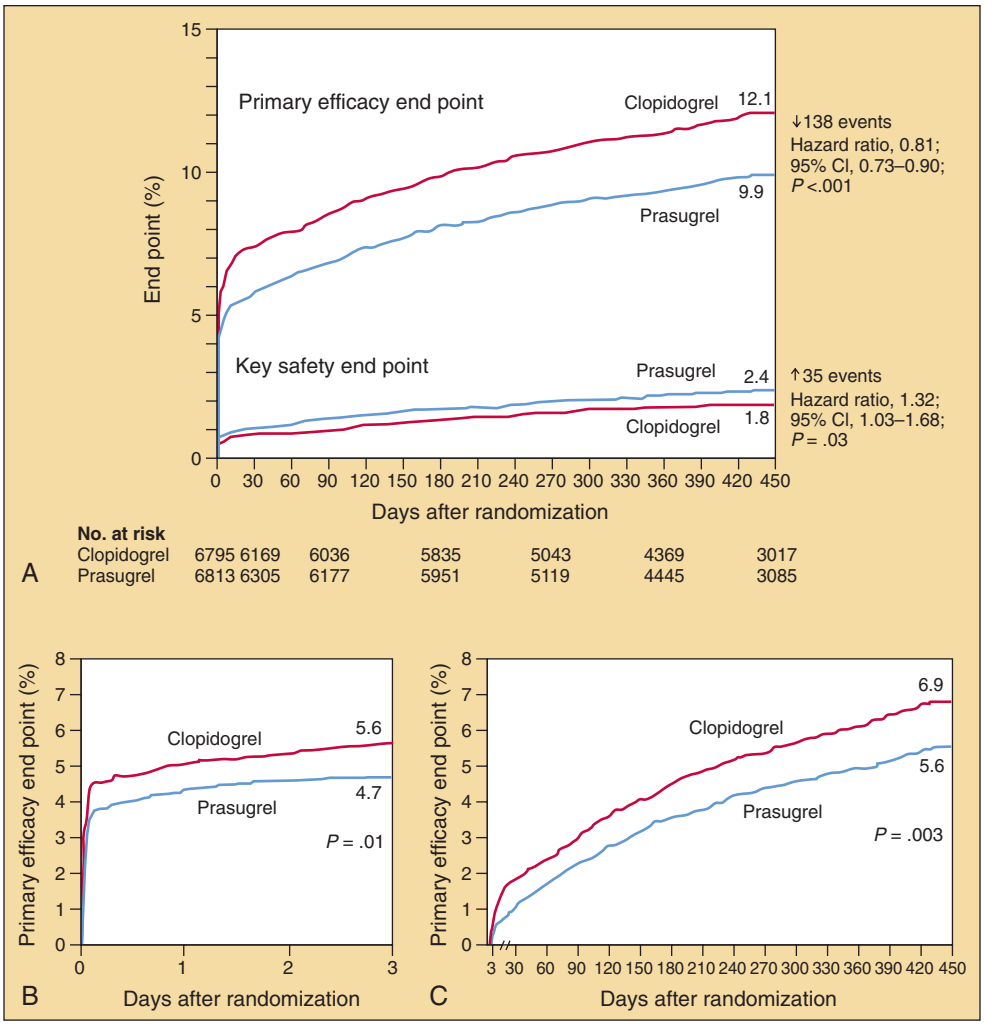

FIGURE 20–8 Primary efficacy and safety endpoints for clopidogrel and prasugrel-treated patients in the TRITON-TIMI 38 Study **(A)**. The primary efficacy endpoint from randomization to day 3 **(B)** and from 3 days to 15 months **(C)** is also shown. *(From Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.)*

stroke occurred in 12.1% of patients receiving clopidogrel and 9.9% of those receiving prasugrel (HR, 0.81; 95% CI, 0.73 to 0.90; $P < .001$). Significant reductions in the rates of MI (9.7% vs. 7.4%; $P < .001$), urgent target vessel revascularization (3.7% vs. 2.5%; $P < .001$) and stent thrombosis (2.4% vs. 1.1%; $P < .001$) in patients randomized to clopidogrel were also observed. Major bleeding (1.8% vs. 2.4%); HR, 1.32), and fatal bleeding (0.1% vs. 0.4%) occurred with greater frequency in patients receiving prasugrel (Fig. 20-8; Table 20-4). A post hoc analyses revealed either no benefit or potential harm from prasugrel compared with clopidogrel treatment in three patient subgroups: patients older than 75 years of age (no net clinical benefit); patients less than 60 kg in body weight (no net clinical benefit); and patients with a history of cerebrovascular events (prior ischemic stroke or transient ischemic attack) (net harm).

In the PLATO trial,[94a] 18,624 patients with ST and NSTE ACS were randomized to received ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300-600 mg loading dose, 75 mg daily thereafter). At 12 months, the primary endpoint consisting of a composite of death from vascular causes, MI, or stroke had occurred in 9.8% and 11.7% respectively, of patients treated with ticagrelor and clopidogrel, (HR, 0.84%; 95% CI, 0.77 to 0.92; $P < .001$). The rate of death from vascular causes was reduced with ticagrelor (4.5% vs. 5.9% with clopdogrel; $P < .001$). Ticagrelor was associated with a higher rate of non–CABG-related major bleeding (4.5% vs. 3.8%; $P = .03$)

SCH530348 is a fully synthetic 3-phenylpyridine analogue of the natural product himbacine. It is a potent and selective inhibitor of the PAR-1 receptor, blocking thrombin-mediated platelet activation. Following oral administration, it is absorbed rapidly with high bioavailability. It is metabolized and eliminated by the biliary-gastrointestinal route and displays a terminal half-life of 126 to 129 hours

In the TRA-PCI trial[95] 1030 patients undergoing nonurgent PCI or coronary angiography with planned PCI were randomized to SCH530348 (10 mg, 20 mg, or 40 mg loading dose) or matching placebo. Patients who subsequently underwent PCI were then assigned to a maintenance dose of 0.5 mg, 1.0 mg or 2.5 mg daily for 60 days. The primary endpoint, TIMI major plus minor bleeding occurred in 1.6%, 2.5% and 4.0%, respectively, receiving 10 mg, 20 mg, and 40 mg compared to 3.3% of patients given placebo (P value for trend = .5786). TIMI major plus minor bleeding during the maintenance phase was reported in 2.2%, 3.6%, and 2.9% in patients receiving 0.5 mg, 1.0 mg, and 2.5 mg, respectively (P value for trend = .7561).

TABLE 20–4 TRITON-TIMI 38 Study: Hemorrhage-Related Endpoints

End Point	Prasugrel (N = 6741)	Clopidogrel (N = 6716)	Hazard Ratio (95% CI)	*P* Value for Prasugrel
	No. of patients (%)			
Non-CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03-1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77-1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09-2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32-1.78)	0.51
Life-threatening*	85 (1.4)	56 (0.9)	1.52 (1.08-2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86-2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12-2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27-1.84)	0.47
Fatal†	21 (0.4)	5 (0.1)	4.19 (1.58-11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87-1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58-2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11-1.56)	0.002
Bleeding requiring transfusion**	244 (4.0)	182 (3.0)	1.34 (1.11-1.63)	<0.001
CABG-related TIMI major bleeding‡	24 (13.4)	6 (3.2)	4.73 (1.90-11.82)	<0.001

The data shown are for patients who received at least one dose of the study drug and for end points occurring within 7 days after the study drug was discontinued or occurring within a longer period if the end point was believed by the local investigator to be related to the use of the study drug. Percentages are Kaplan-Meier estimates of the rate of the end point at 15 months. Patients could have more than one type of end point. CABG, coronary-artery bypass grafting.

*The most frequent sites of life-threatening bleeding were gastrointestinal sites, intracranial sites, the puncture site, and retroperitoneal sites.

†One patient in the clopidogrel group had a fatal gastrointestinal hemorrhage while receiving the study medication, but hemoglobin testing was not performed and, therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied and the data do not appear in this table.

**Transfusion was defined as any transfusion of whole blood or packed red cells.

‡For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel or clopidogrel before undergoing CABG: 179 and 189, respectively. The ratio is the odds ratio, rather than the hazard ratio, and was evaluated with the use of the Cochran-Mantel-Haenszel test.

From Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.

PLATELET PERFORMANCE MEASUREMENT TOOLS AND CLINICAL OUTCOMES

A patient-specific or tailored approach to the management of ACS acknowledges inherent genotypic, phenotypic, and pharmacologic variability in drug therapy. While large-scale advanced biomarker and pharmacogenetic studies are likely to better characterize and identify patients at risk for hemorrhagic complications, recurring ischemic/thrombotic events, drug failures and off-target toxicities, platelet performance measurement tools, if readily available to practicing clinicians and capable of providing information that could be translated directly to therapy decision, would also impact care meaningfully (reviewed in reference 96).

For patients with CAD, the potential utility of measuring platelet function includes monitoring antiplatelet therapy and predicting clinical outcomes. For example, although aspirin reduces the risk of thrombotic events in high-risk patients by about 25%, 10% to 20% of treated patients will have another thrombotic event during long-term follow-up. These patients might require additional platelet-directed therapy with clopidogrel or other agents. A key question relating to this issue is whether standardized laboratory tests assessing the platelet response to aspirin or clopidogrel can predict clinical "resistance" (Table 20-5).

Correlating Measures of Platelet Performance with Clinical Outcomes

Studies attempting to correlate measures of platelet function and its attenuation with drug therapies with clinical outcomes have often focused on a receptor-signaling pathway or reactivity to agonists (activation or aggregation). Most commonly, platelet function has been measured by the degree of aggregation in response to a specific concentration of agonist, but platelet-fibrin interactions also have been measured, as has platelet activation via measures of platelet and soluble P-selectin, urinary thromboxane metabolites, and other markers. These measures have been used primarily to assess relationships between platelet function and stent thrombosis or major adverse cardiac events (MACE) in patients treated with PCI.

The overall number of patients studied within investigations designed specifically to link ex vivo response variability to clinical resistance (outcome) is modest.[97-116]

The International Society on Thrombosis and Haemostasis Working Group on Aspirin Resistance[117] has stated that a clinically meaningful definition of resistance should be based on data linking therapy-dependent laboratory tests to clinical outcomes. The group also noted that the correct treatment, if any, of aspirin resistance is unknown, given that no study has addressed the clinical effectiveness of altering therapy based specifically on laboratory findings of resistance. Other than within clinical trials, which the group encouraged strongly, it is currently not appropriate to test patients for aspirin or clopidogrel resistance or to change therapy based on such testing.

A clinical trial designed to investigate antiplatelet resistance would require sufficient power to answer two key questions:

1. Which simple, inexpensive, reproducible and rapid test of platelet function (or combination of tests) best predicts clinical outcomes of antiplatelet therapy

TABLE 20–5 Current Clinical Tests of Platelet Function

Function	Advantages	Drawbacks	Predicts Outcomes?	Able to Monitor: Aspirin	Thieno-pyridines	GP IIb/IIIa Inhibitors
Cessation of Blood Flow by Platelet Plug (for PFA, at high shear)						
Bleeding Time	In vivo, physiologic	Nonspecific, not sensitive, scarring, high interoperator CV	No	No	No	No
PFA-100	Simple, rapid, small sample volume, no preparation, whole-blood assay	No instrument adjustment, depends on vWF, Hct	Yes	Yes	NR	NR
Platelet-Platelet Aggregation						
Platelet aggregometry: turbidimetric	Historical "gold standard"	Variable reproducibility, expensive, large sample volume, sample preparation, time-consuming	Yes	Yes*†	Yes†	Yes
Platelet aggregometry: impedance	Whole-blood assay	Expensive, large sample volume, sample preparation, time-consuming	Yes	Yes*	Yes†	Yes
VerifyNow	Simple, rapid, POC; small sample volume, no sample preparation, whole-blood assay	No instrument adjustment	Yes	Yes‡	Yes§	Yes‖
Plateletworks	Little sample preparation, whole-blood assay	Not well studied	No	Yes*	Yes†	Yes
Shear-Induced Platelet Adhesion						
Impact cone and plate(let) analyzer	Simple, rapid, POC, small sample volume, high shear, whole-blood assay	Not widely available	No	Yes*	Yes†	NR
Platelet Contribution to Clot Shear Elasticity						
Thromboelastogram	POC, whole-blood assay, platelet-clot formation and clot lysis data	Limited studies	Yes	Yes*	Yes†	Yes
Basis: Activation-Dependent Changes in Platelet Surface						
Platelet surface P-selectin, platelet surface activated GP IIb/IIIa, leukocyte-platelet aggregates	Small sample volume, whole-blood assay	Sample preparation, expensive, requires flow cytometer and experienced staff	Yes	Yes*	Yes†	Yes
Activation-Dependent Signaling						
VASP phosphorylation	Small sample volume, whole-blood assay, P2Y12-dependent	Sample preparation, expensive, requires flow cytometer and experienced staff	Yes	No	Yes	No
Activation-Dependent Release from Platelets						
Platelet-derived microparticles	Small sample volume, whole-blood assay	Sample preparation, expensive, requires flow cytometer and experienced staff	No	No	No	No
Serum thromboxane B_2	COX-1-dependent	Indirect, not platelet-specific	No	Yes	No	No
Urinary 11-dehydro-thromboxane B_2	COX-1-dependent	Indirect, not platelet-specific, depends on renal function	Yes	Yes	No	No
Plasma soluble CD40 ligand	Most CD40 ligand is platelet-derived	Plasma separation can cause artifactual platelet activation	Yes	No	No	No
Plasma GP V	Platelet-specific	Plasma separation can cause artifactual platelet activation, reflects only thrombin-mediated platelet activation	No	No	No	No
α-Granule constituents**	Reflect platelet secretion	Plasma separation can cause artifactual platelet activation, endothelial cells also secrete P-selectin	No	No	No	No

COX, cyclooxygenase; CV, coefficient of variation; GP, glycoprotein; Hct, hematocrit; NR, not recommended; PFA, platelet function analyzer; POC, point of care; VASP, vasodilator-stimulated phosphoprotein; vWF, von Willebrand factor.

From Gurbel PA, Becker RC, Mann KG, et al: Platelet function monitoring in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1822-1834.

for specific individuals with specific indications for treatment?

2. Are individual outcomes improved when treatment is changed in response to the test(s) results?

A basic objective is to develop absolute or relative thresholds (upper and lower) for test results, similar to the practice of tailoring warfarin therapy according to the standardized INR. The landscape for developing an equivalent testing strategy for platelet-directed therapy is considerably more complex, with the concomitant use of several drugs with different mechanisms of action and multiple testing platforms.

Clinical trials also must investigate, in patients with known resistance or drug failure, or both, the potential

TABLE 20–6	Relation of Aspirin Responsiveness to Clinical Outcomes			
Study	**n**	**Patients**	**Method**	**Results**
Mueller[112]	100	PVD	Platelet aggregation (whole blood)	87% increase in reocclusion
Eikelboom[113]	976	High-risk CAD	Urinary 11-dehydro TxB_2	Increase in MI/stroke/death with increased TxB_2
Gum[114,115]	325	Stable CAD	Light transmittance aggregometry	3.12-fold increase in MI/stroke/death
Chen[116]	151	PCI	RPFA	2.9-fold increase in myocardial necrosis
Grotemeyer[111]	180	Post-CVA	Platelet aggregates	10-fold increase in vascular events

CAD, coronary artery disease; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RPFA, rapid platelet function analyzer; Tx, thromboxane.

From Gurbel PA, Becker RC, Mann KG, et al: Platelet function monitoring in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1822-1834.

benefit of dose adjustment or supplementary treatments with different pharmacodynamic profiles. For example, if a patient with CAD suffers an event while already taking aspirin, it might be more effective to increase the dose of aspirin, add a thienopyridine agent for additional secondary prevention, or both, rather than simply substituting drugs.

Aspirin Response Variability

Several studies[111,112] suggested a relation between high platelet reactivity among patients receiving aspirin and an increased risk of vascular events (Table 20-6). In patients enrolled in the HOPE trial, Eikelboom and coworkers[113,118] showed a relation between high urinary 11-dehydrothromboxane B_2 levels, a measure of platelet thromboxane A_2 generation, and the risk for subsequent ischemic events. Chen and colleagues[116] showed a relation between high platelet reactivity measured by Ultegra Rapid Platelet Function Assay-ASA and periprocedural myonecrosis in patients undergoing PCI. The potential clinical impact of aspirin response variability was evaluated in the CHARISMA study.[118] Urinary 11-dehydrothromboxane $ß_2$ concentrations were measured in 3261 aspirin-treated patients at least 1 month after they had been randomized to placebo or clopidogrel baseline; thromboxane generation in the highest quartile was associated with an increased risk of stroke, MI, or cardiovascular death compared with the lowest quartile (adjusted hazard ratio, 1.66; 95% CI, 1.66; 95% DI, 1.06 to 2.61; $P = .003$). Randomization to clopidogrel did not reduce the hazard of cardiovascular risk in patients within the highest quartile of 11-dehydrothromboxane $ß_2$.

Using light transmittance aggregometry (LTA), Gum and colleagues assessed the relation between aspirin resistance and the composite outcome of death, MI, or stroke over a mean 1.8 years of follow-up in 326 patients with stable CAD taking 325 mg of aspirin for ≥1 week before enrollment.[114,115] In all, 5.2% of patients were considered aspirin-resistant (≥70% mean aggregation in response to 10 µmol/L ADP and ≥20% aggregation after incubation with 0.5 mmol/L arachidonic acid). During follow-up, 24% of aspirin-resistant patients had an event versus 10% of nonresistant patients ($P = .03$), but the relationships between aspirin resistance (as a categorical or continuous variable) and the component clinical events were not statistically significant. After adjustment for several risk factors, aspirin resistance was an independent predictor of long-term adverse events.

Using the PFA-100 analyzer to measure aspirin-mediated platelet inhibition, several studies have reported increased event rates in patients with a profile of aspirin resistance.[119,120] This method has several limitations, however, including poor correlation to other measures of platelet performance and dependence on von Willebrand factor level and activity and platelet count. The PFA-100 method also uses collagen and epinephrine as agonists, neither of which is specific for COX-1 activity, the target of aspirin. A major limitation of all published studies of aspirin resistance is a lack of serial platelet-function measurements, particularly since the degree of aspirin resistance can fluctuate over time and can be affected by aspirin dose.[121,122] While a patient-specific or tailored dosing strategy to aspirin based on platelet measurement parameters has not been investigated, the CURRENT-OASIS 7 study may provide valuable insights.[123]

Clopidogrel Response Variability

Published studies investigating the association between platelet reactivity to ADP (indicative of clopidogrel responsiveness) and the occurrence of ischemic events have involved patients undergoing PCI, with most employing LTA measurement of platelet function (Table 20-7).[97-100,102,104,106,108] These studies with generally small populations have reported links between clopidogrel-induced platelet inhibition, post-treatment platelet reactivity, periprocedural myonecrosis, stent thrombosis, and recurrent ischemic events.

Matetzky and colleagues examined 60 consecutive patients with MI undergoing primary PCI with stenting,[98] all of whom received clopidogrel, aspirin, and eptifibatide. Ten consecutive patients undergoing primary angioplasty without stenting and given no clopidogrel were the controls. Platelet aggregation by LTA in response to 5 µmol/L ADP and 10 µmol/L epinephrine, and by cone and plate(let) analysis expressed as the percent surface coverage by platelets and average size of surface-bound aggregates, was determined. When treated patients were grouped into quartiles by percent reduction in ADP-induced aggregation at day 6 versus baseline (before clopidogrel administration), the responses varied from a mean aggregation of 103% of the baseline value in the first quartile (considered clopidogrel-resistant) to only 33% of the baseline value in the fourth quartile ($P < .01$ across groups). This variability persisted for epinephrine-induced aggregation and aggregate size measurements. Over 6-month follow-up, 7 of the 8 major cardiac events occurred in the clopidogrel-resistant group; 40% of the first-quartile patients had another ischemic event. No correlation between platelet inhibition measured by the cone and plate(let) device and clinical outcomes was reported.

In the CLEAR-PLATELETS study, ADP-induced aggregation was measured serially over 18 to 24 hours in 120 patients undergoing stenting treated with 300 or 600 mg of clopidogrel or with eptifibatide.[103] Patients with MI according to creatine kinase-MB release had significantly greater mean platelet reactivity to ADP compared with patients without MI, suggesting a threshold of mean platelet aggregation that might be used as a reference point for future studies.

The relation of platelet reactivity and stent thrombosis has also been investigated, with most studies reporting that high

TABLE 20–7 Relation of Platelet Reactivity to ADP/Clopidogrel Nonresponsiveness to Clinical Outcomes

Study	n	Results	Clinical Relevance
Matetzky	60	Clopidogrel nonresponsiveness; STEMI patients loaded with clopidogrel	Ischemic events (6 m)
Geisler	379	↑ Pre-procedural platelet aggregation, CAD patients loaded with clopidogrel	Ischemic events (3 m)
Gurbel	192	↑ Post-procedural platelet aggregation, patients loaded with clopidogrel at time of elective PCI	Ischemic events (6 m)
Gurbel	120	↑ Periprocedural mean platelet aggregation; patients loaded with clopidogrel at time of elective PCI ± eptifibatide	In-hospital post-PCI myonecrosis, inflammation marker release
Bliden	100	↑ Pre-procedural platelet aggregation; patients on maintenance clopidogrel therapy pre-elective PCI	Ischemic events (12 m)
Cuisset	106	↑ Pre-procedural platelet aggregation; NSTEMI ACS patients treated with clopidogrel pre-PCI	Ischemic events (1 m)
Lev	120	Clopidogrel and aspirin nonresponsiveness; patients loaded with clopidogrel immediately after elective PCI	In-hospital post-PCI myonecrosis
Hochholzer	802	↑ Pre-procedural platelet aggregation; patients treated with clopidogrel pre-elective PCI	Ischemic events (1 m)
Barragan	36	↑ P2Y12 reactivity ratio by VASP-P measurement	Stent thrombosis
Gurbel	120	↑ P2Y12 reactivity ratio by VASP-P measurement, platelet aggregation, and ADP-stimulated GP IIb/IIIa expression	Stent thrombosis
Ajzenberg	49	↑ Shear-induced platelet aggregation	Stent thrombosis
Wong	264	↓ Platelet inhibition by VerifyNow P2Y12 assay	Stent thrombosis
Buonamici	804	↑ Post-treatment platelet aggregation	Stent thrombosis

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post-treatment platelet activity as determined by various methods is associated with stent thrombosis.[102,107-110] However, the reported measures varied widely in patients with and without thrombosis. Further studies lend strong support to the association between high post-treatment platelet reactivity to ADP and the occurrence of post-stenting ischemic events. Hochholzer and associates studied 802 patients undergoing stenting treated with 600 mg clopidogrel and found that post-treatment platelet aggregation above the median had 6.7-fold risk of 30-day major adverse cardiac event occurrence.[101] In another study of 804 patients undergoing stenting, Buonamici and coworkers demonstrated that stent thrombosis was more prevalent in patients with post-treatment platelet aggregation ≥70% in response to 10 µmol/L ADP stimulation.[102] A patient-specific approach to clopidogrel loading dose based on vasodilator-stimulated phosphoprotein (VASP) phosphorylation was investigated in a study of 162 patients by Bonello and colleagues.[124]

The VASP index was calculated 24 hours after a first 600-mg dose of clopidogrel. All patients with a VASP index above 50% were then randomly assigned to a control group (PCI conducted without additional clopidogrel or a group who received up to 3 additional 600 mg disease given at 24-hour increments with the goal of achieving a VASP index below 50%. Dose adjustment successfully achieved the specified laboratory-based goal of treatment in 67 of 87 patients (86%). Eight major adverse events were recorded during the 30-day follow-up—with no events in the VASP-directed group.

Glycoprotein IIb/IIIa Receptor Antagonist Response Variability

The GOLD study reported a relation between inhibition of platelet function and MACE. The study included 500 patients undergoing PCI and used the VerifyNow GP IIb/IIIa assay.[125] In all, 25% of patients did not achieve >95% platelet inhibition 10 minutes after administration of a GP IIb/IIIa inhibitor. These patients had a significantly higher incidence of MACE (14.4% vs. 6.4% for patients with ≥95% inhibition; $P = .006$). In multivariate analysis, platelet inhibition ≥95% 10 minutes after GP IIb/IIIa inhibitor administration was independently associated with a 50% lower risk of MACE.

POST-TREATMENT PLATELET RESPONSE AND LONG-TERM ISCHEMIC EVENTS

There is preliminary evidence for a potential threshold of platelet reactivity, as measured by LTA after ADP stimulation that is associated with an increased risk of postdischarge ischemic events after PCI. In the PREPARE POST-STENTING study, the first investigation linking high post-treatment platelet reactivity to ADP and the occurrence of post-discharge ischemic events, a threshold of about 50% periprocedural platelet aggregation in response to 20 µmol/L ADP was associated with the occurrence of ischemic events during 6-month follow-up.[97] Similarly, in another study, about 40% platelet aggregation in response to 20 µmol/L ADP was associated with the occurrence of stent thrombosis.[105] In a third study by the same group, a threshold of about 40% preprocedural platelet aggregation in response to 5 µmol/L ADP among patients receiving long-term clopidogrel and aspirin therapy before undergoing stenting was associated with the occurrence of ischemic events over the ensuing 12 months.[108] The latter study suggests the potential utility of a pre-PCI platelet reactivity measurement as a potential marker of long-term ischemic events. The timing and method of measuring platelet function that best correlates with patient outcomes is under investigation.

The available data may provide a "testable" level of post-treatment platelet reactivity for future studies, similar to the INR ranges established for warfarin therapy. The available data suggest that adequate protection against ischemic events with aspirin and clopidogrel therapy may be achieved by low to moderate levels of post-treatment platelet reactivity in the majority of patients. These findings have implications on bleeding risks as well during dual antiplatelet therapy that

may accompany markedly low levels of post-treatment platelet reactivity. Currently, the relation of bleeding to levels of ADP-induced aggregation is unknown. Future studies will be required to determine whether there is a "therapeutic window" for oral antiplatelet agents akin to the INR used to determine efficacy and safety parameters for warfarin therapy.

SUMMARY

The contribution of platelets to the initiation, progression, and clinical expression of atherothrombotic coronary artery disease to include ACS is incontrovertible. Decades of research, coupled with large-scale clinical trials, support evidence of benefit, but similarly highlight the importance of patient characteristics in determining the risk of hemorrhagic events. The development of increasingly potent platelet antagonists will potentially narrow the safety window for combined pharmacotherapies, and introduce a new field of acquired vascular disorders stemming from altered platelet-mediated repair.

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CHAPTER 21

Nonresponsiveness to Antiplatelet Therapy

Wai-Hong Chen and Daniel I. Simon

Platelets play a pivotal role in mediating thrombotic complications of atherosclerotic vascular disease. Oral antiplatelet agents are the cornerstone of pharmacologic therapy for preventing ischemic events of atherothrombotic disease. Aspirin and clopidogrel, by blocking thromboxane A_2 (TXA_2)- and adenosine diphosphate (ADP)-induced platelet activation pathways, respectively, are the most commonly used oral antiplatelet drugs in clinical practice. Variability in the response to antiplatelet drugs has been recognized for decades. Antiplatelet drug resistance or *nonresponsiveness* is used to describe the clinical observation of the inability of the antiplatelet agent to prevent thrombotic vascular events or the laboratory phenomenon of reduced effect of the antiplatelet agent on one or more tests of platelet function.

Using nonstandardized definitions of nonresponsiveness based on a variety of platelet function tests including, among others, light transmission aggregometry (LTA), impedance aggregometry, urinary metabolites of TXA_2, flow cytometry, fibrinogen-coated bead agglutination, thromboelastography, and shear-induced measures of platelet function, the prevalence of aspirin nonresponsiveness ranges from 5% to 60%[1] and the prevalence of clopidogrel nonresponsiveness ranges from 17% to 32%.[2] Although LTA is frequently cited as the "gold standard" for platelet function testing, there is lack of consensus on whether percent inhibition of a particular platelet function test or persistent high platelet reactivity is the more appropriate determinant of nonresponsiveness. The mechanisms of aspirin and clopidogrel resistance are incompletely defined. Multiple cellular, clinical, and genetic factors likely contribute to both aspirin[1] and clopidogrel[3] nonresponsiveness (Figs. 21-1 and 21-2). Nonadherence to drug regimens (i.e., noncompliance) is likely responsible for a significant proportion of nonresponsiveness as assessed by platelet function testing.[4,5] Increasing clopidogrel dose[6,7] or hepatic cytochrome P-450 (CYP450) activity enhances the platelet inhibitory response of clopidogrel by increasing the concentration of the active metabolite (Fig. 21-3).[8] Conditions or risk factors associated independently with clopidogrel nonresponsiveness include congestive heart failure, body weight (>100 kg), myocardial infarction (MI) presentation, and diabetes mellitus.[9] Genetic polymorphisms, particularly of genes responsible for the metabolism of clopidogrel, such as the *2 allele of CYP4502C19, result in loss-of-function leading to reduced conversion of clopidogrel to its active metabolite, and are associated with a higher rate of adverse cardiovascular events in patients presenting with acute coronary syndromes and after percutaneous coronary intervention (PCI) (Fig. 21-4).[10-13] The CYP2C19*2 allele is common in the general population (approximately 30% of whites, 40% of African-Americans, and more than 55% of East Asians)[13,14] and, therefore, is likely to have clinical significance that will need to be explored in future clinical trials. An additional limitation of clopidogrel involves drug-drug interactions. Use of drugs that inhibit the activity of CYP2C19, including several of the proton pump inhibitors (PPI), could result in reduced drug levels of the active metabolite and a possible reduction in clinical efficacy. A retrospective cohort study of more than 16,700 patients who received clopidogrel post-stenting reported an increase in the 1-year risk of cardiovascular events in patients taking omeprazole, esomeprazole, pantoprazole, and lansoprazole on top of clopidogrel as compared with patients not taking a PPI, indicating that the risk may be a class effect (hazard ratio [HR] 1.51; 95% confidence interval [CI] 1.39-1.64; $P < .0001$).[15] The risk of adverse outcomes associated with the concomitant use of clopidogrel and PPIs has been confirmed in additional studies, and in general is also found in the placebo group of clopidogrel trials.[16,17] Such data have prompted a specific label change for clopidogrel indicating that concomitant use of drugs that inhibit CYP2C19 (e.g., omeprazole and other PPIs) should be discouraged.

In contrast to clopidogrel, there is little evidence that increasing aspirin dose influences responsiveness to aspirin as assessed by tests of platelet function or clinical outcomes,[18] except possibly for diabetic patients in whom resistance may be partially overcome by higher aspirin doses.[19]

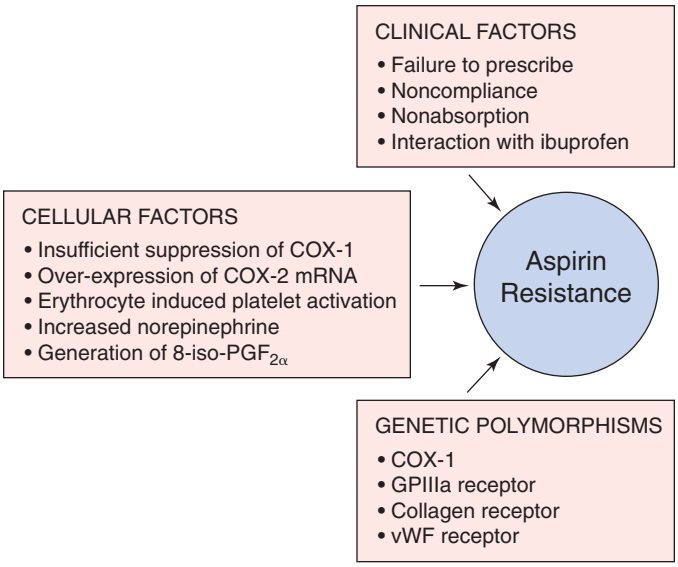

FIGURE 21–1 Some of the possible mechanisms of apparent aspirin resistance. COX, cyclooxygenase; GP, glycoprotein; vWF, von Willebrand Factor. *(From Bhatt DL: Aspirin resistance: More than just a laboratory curiosity. J Am Coll Cardiol 2004; 43:1127-1129.)*

The preparation of aspirin does not appear to affect platelet inhibitory responses in the chronic phase; however, attenuated platelet inhibition by low-dose (81 mg) enteric-coated preparations has been observed within the first week.[20]

ASPIRIN NONRESPONSIVENESS AND CLINICAL OUTCOMES

An increasing number of prospective studies linking laboratory measures of antiplatelet drug nonresponsiveness to adverse clinical outcomes have been reported. It is important to note that there are major limitations of the currently available data. The number of patients studied in all of the reports is small. The study designs are not adequate for controlling confounding variables. The dosage of aspirin varied, treatment compliance was not verified, and the definition of aspirin resistance is not uniform. Key historical studies are summarized below.

Grotemeyer and coworkers[21] determined aspirin responsiveness in 180 stroke patients 12 hours after an oral intake of 500 mg aspirin. Patients with a platelet reactivity index of less than or equal to 1.25 were categorized as aspirin responders while those with an index of greater than or equal to 1.25 were defined as being secondary aspirin nonresponders (i.e., aspirin-resistant). All patients were prescribed aspirin 500 mg three times daily and were followed for 24 months. Stroke, MI, or vascular death were major outcome measures. The incidence of aspirin resistance was 33%. Complete follow-up was obtained in 174 patients (96%). Major events were noted in 29 patients: 5 (4.4%) in the aspirin-responder group versus 24 (40%) in the aspirin-resistant group ($P < .0001$).[1]

Mueller and coworkers[22] studied 100 patients with intermittent claudication undergoing elective percutaneous balloon angioplasty. Aspirin was prescribed at a dose of 100 mg daily. Using corrected whole blood aggregometry they defined a normal response to aspirin as at least 20% reduction in platelet function with both ADP and collagen as agonists. Fluctuations in aspirin responsiveness among the studied population were noted on serial monitoring. The incidence of aspirin resistance was about 60% at each time point of measurement. At 52-week follow-up, 8 patients in the aspirin-resistance group were noted to have reocclusion at the angioplasty site, compared with none of the patients with a normal response to aspirin (87% increase in risk, $P = .0093$).

Eikelboom and coworkers[23] performed a nested case-control study on 976 aspirin-treated patients, with documented or at high-risk of cardiovascular disease, from the Heart Outcomes Prevention Evaluation database. Aspirin

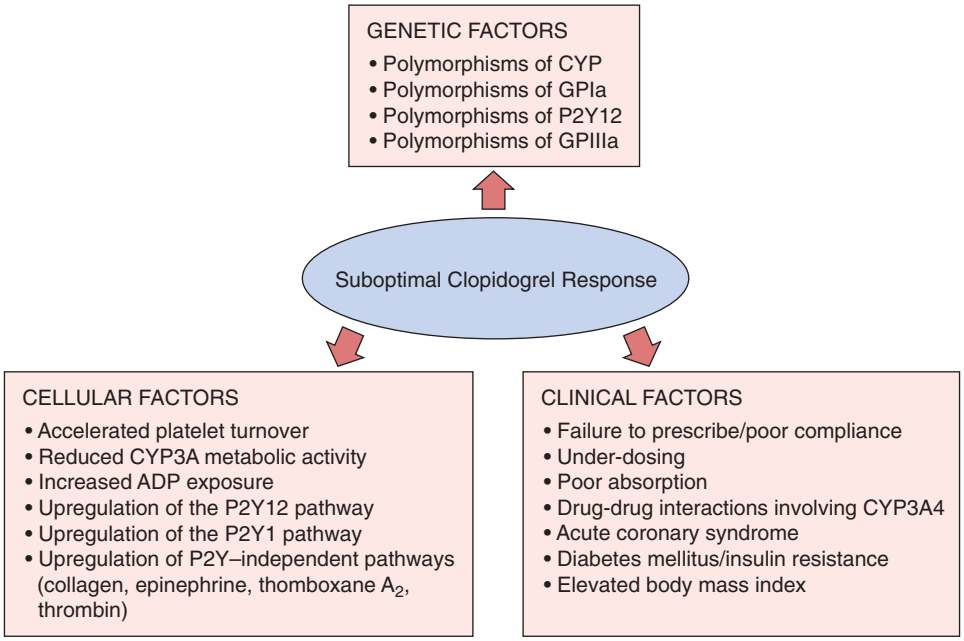

FIGURE 21–2 Proposed mechanisms leading to variability in individual responsiveness to clopidogrel. ADP, adenosine diphosphate; CYP, cytochrome P-450; GP, glycoprotein. *(From Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al: Variability in individual responsiveness to clopidogrel: Clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505-1516.)*

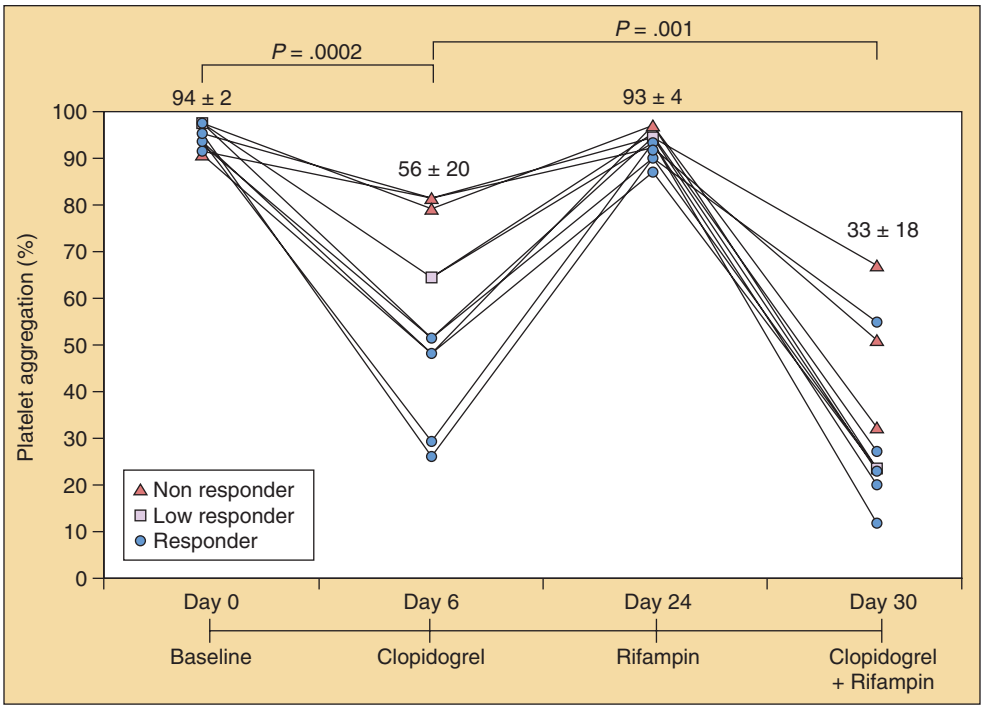

FIGURE 21–3 Percent platelet aggregation in 10 healthy volunteers after clopidogrel, rifampin, and clopidogrel plus rifampin. *(From Lau WC, Gurbel PA, Watkins PB, et al: Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation 2004;109:166-171.)*

responsiveness was divided into quartiles by urinary 11-dehydrothromboxane B_2 levels, a marker of in vivo thromboxane generation. After 5 years of follow-up, those patients in the highest quartile had 1.8-fold increase in risk for the composite of MI, stroke, or cardiovascular death (odds ratio [OR] 1.8; 95% CI 1.2-2.7; $P = .009$; Fig. 21-5) when compared to those in the lowest quartile. The risks of MI (OR 2.0; 95% CI 1.2-2.7; $P = .006$) and cardiovascular death (OR 3.50; 95% CI 1.7-7.4; $P < .001$) were likewise significantly increased.

Gum and colleagues[24] enrolled 326 stable patients with cardiovascular disease taking aspirin 325 mg daily for 7 days or less and defined aspirin resistance as a mean aggregation of more than 70% with 10 μm ADP and a mean aggregation of more than 20% with 0.5 mg/mL arachidonic acid by optical platelet aggregation. Aspirin resistance was noted in 17 patients (5.2%). After a mean follow-up of 1.8 years, major events (death, MI, or stroke) occurred in 4 (24%) patients in the aspirin-resistant group, compared with 30 (10%) patients in the aspirin-sensitive group ($P = .03$). The Kaplan-Meier time-to-event curves for event-free survival showed late divergence of the event curves that remained to be explained (Fig. 21-6). Multivariate analysis demonstrated that, in addition to other risk factors such as increasing age, history of congestive heart failure, and elevated platelet count, aspirin resistance was an independent predictor of adverse outcomes (hazard ratio [HR] 4.14; 95% CI 1.42-12.06; $P = .009$).

Chen and coworkers[25] tested aspirin responsiveness in patients undergoing elective PCI treated with aspirin at 80 to 300 mg daily for at least 7 days. Using the aggregation-based point-of-care Rapid Platelet Function Assay-Aspirin (VerifyNow Aspirin), 29 (19.2%) out of the 151 enrolled patients were found to be aspirin-resistant, as defined by an aspirin reaction unit (ARU) of greater than 550. Despite clopidogrel pretreatment with a loading dose of 300 mg at least 12 hours prior to the intervention and procedural anticoagulation using heparin, patients with aspirin resistance had a 2.9-fold increased risk of myocardial necrosis determined by creatine kinase-MB elevation when compared with aspirin-sensitive patients.

After reporting the predictors and prevalence of aspirin resistance among 468 stable patients with coronary artery disease using VerifyNow Aspirin,[26] Chen and coworkers followed this cohort prospectively and found that after a mean follow-up of 379 ± 200 days, patients with aspirin resistance ($n = 128$; 27.4%) were at increased risk of the composite outcome of cardiovascular (CV) death, MI, unstable angina requiring hospitalization, stroke, and transient ischemic attack compared with patients who were aspirin-sensitive (15.6% vs. 5.3%; HR 3.12; 95% CI 1.65-5.91; $P < .001$).[27] Cox proportional hazard regression modeling identified aspirin resistance, diabetes, prior MI, and a low hemoglobin to be independently associated with major adverse long-term outcomes (HR for aspirin resistance 2.46; 95% CI 1.27-4.76; $P = .007$).

A systematic review and meta-analysis of aspirin "resistance" and risk of cardiovascular morbidity is highlighted in Figure 21-7.[28] Twenty studies totaling 2930 patients with cardiovascular disease and treated with aspirin 75 to 325 mg were included. Compliance was confirmed directly in only 14 out of 20 studies and 28% were classified as aspirin resistant using a variety of ex vivo platelet function assays and non-uniform definitions of resistance. Aspirin resistant compared to aspirin sensitive patients were at a greater risk of any cardiovascular event (OR 3.85; 95% CI 3.08-4.80), death (OR 5.9; 95% CI 2.28-15.72), or acute coronary syndrome (OR 4.06; 95% CI 2.96-5.56).

CLOPIDOGREL NONRESPONSIVENESS AND CLINICAL OUTCOMES

The first prospective study linking clinical outcome to clopidogrel responsiveness was reported by Barragan and coworkers.[29] Using assay of vasodilator-stimulated phosphoprotein phosphorylation (VASP), a marker of platelet inhibition that

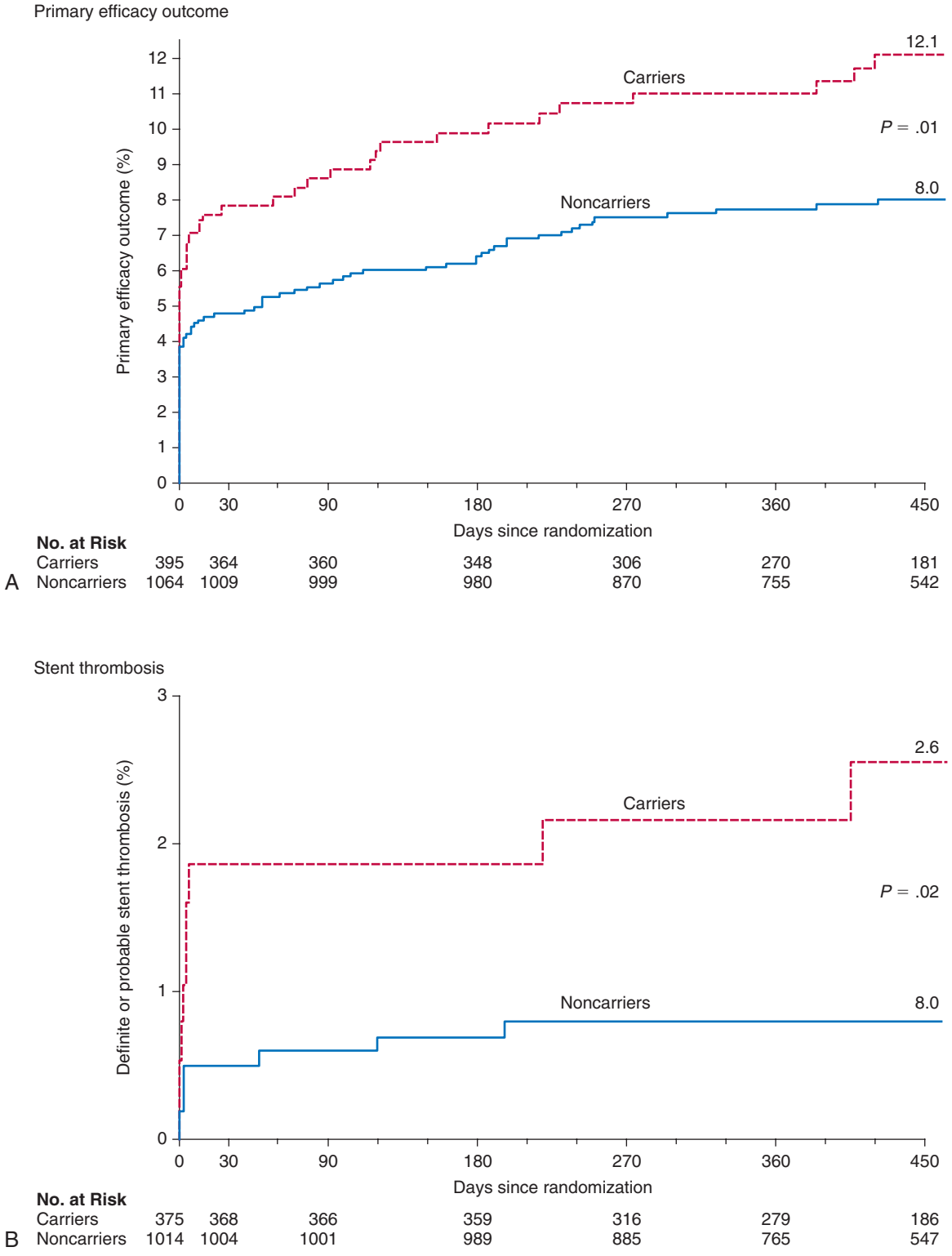

FIGURE 21–4 A, Association between status as a carrier of a *CYP2C19* reduced-function allele and the primary efficacy outcome or stent thrombosis in subjects receiving clopidogrel. Among 1459 subjects who were treated with clopidogrel and could be classified as *CYP2C19* carriers or noncarriers, the rate of the primary efficacy outcome (a composite of death from cardiovascular causes, myocardial infarction, or stroke) was 12.1% among carriers, compared with 8.0% among noncarriers (hazard ratio for carriers, 1.53; 95% confidence interval, 1.07-2.19). **B,** Among 1389 subjects treated with clopidogrel who underwent PCI with stenting, the rate of definite or probable stent thrombosis (a key prespecified secondary outcome, defined as per the Academic Research Consortium) was 2.6% among carriers and 0.8% among noncarriers (hazard ratio, 3.09; 95% CI, 1.19-8.00). *(From Mega JL, Close SL, Wiviott SD, et al: Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-362.)*

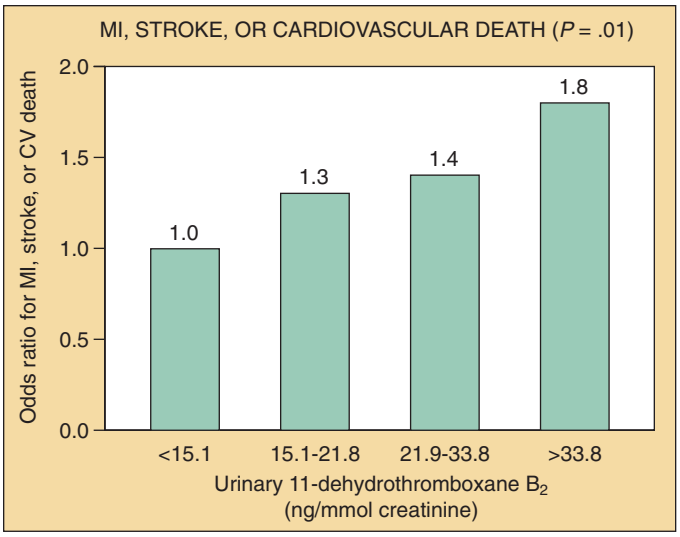

FIGURE 21–5 Association between quartiles of 11-dehydrothromboxane B_2 and composite of myocardial infarction (MI), stroke, or cardiovascular (CV) death after adjustment for baseline differences between cases and control subjects. *P* value is for trend of association. *(From Eikelboom JW, Hirsh J, Weitz JI, et al: Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002;105:1650-1655.)*

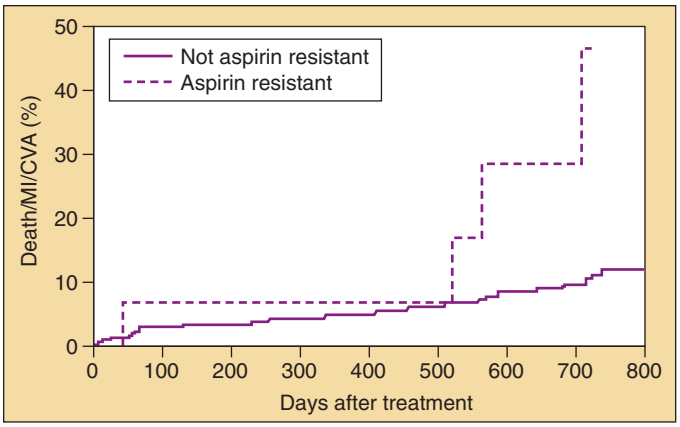

FIGURE 21–6 Kaplan-Meier time-to-event-curves for event-free survival based on aspirin sensitivity among 326 stable cardiovascular patients. CVA, cerebrovascular accident; MI, myocardial infarction. *(From Gum PA, Kottke-Marchant K, Welsh PA, et al: A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003;41:961-965.)*

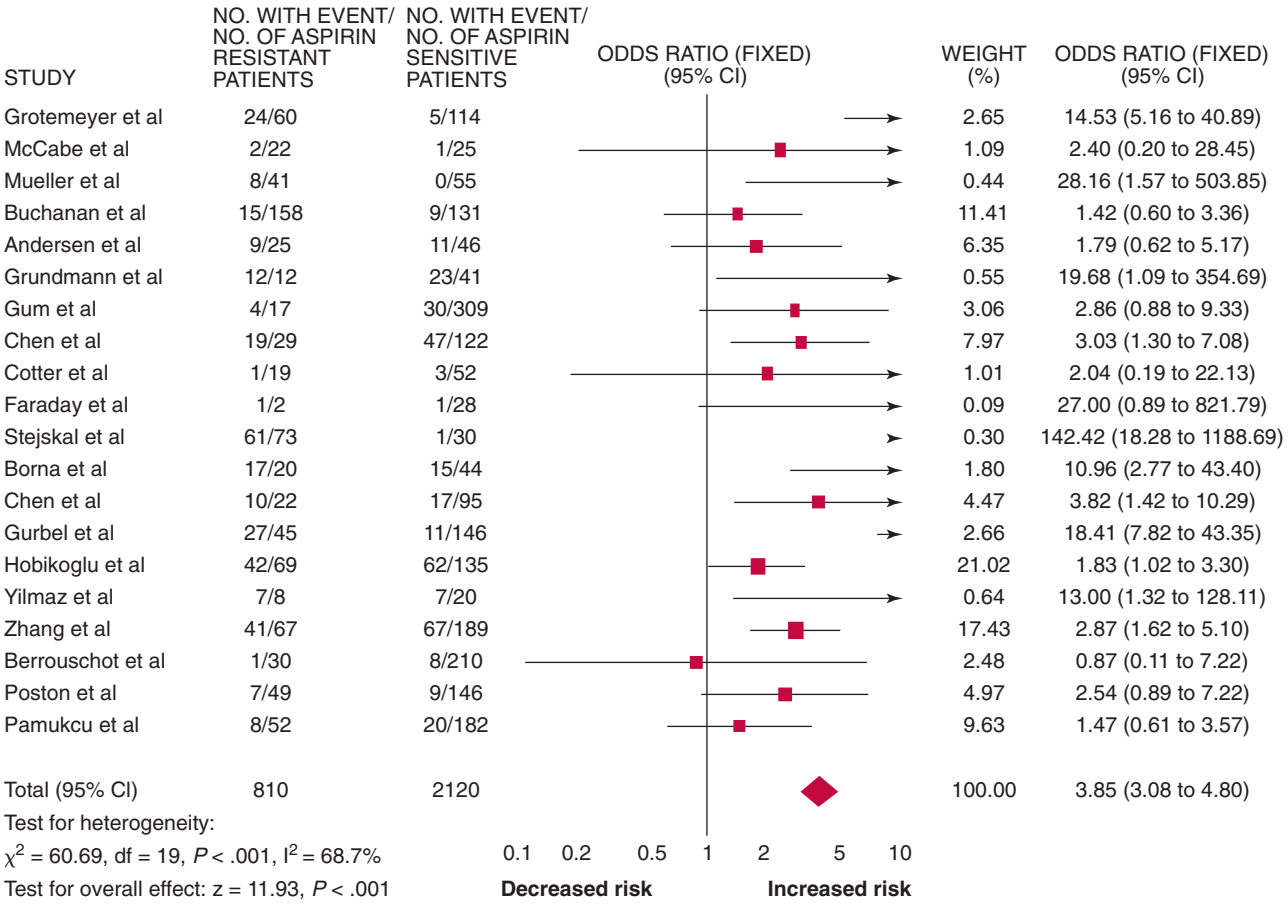

FIGURE 21–7 Risk of any cardiovascular event in aspirin resistant patients. Twenty studies totaling 2930 patients with cardiovascular disease and treated with aspirin 75 to 325 mg were included. Aspirin-resistant compared to aspirin-sensitive patients were at a greater risk of any cardiovascular event (odds ratio, 3.85; 95% confidence interval, 3.08-4.80). *(From Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR: Aspirin "resistance" and risk of cardiovascular morbidity: Systematic review and meta-analysis. BMJ 2008;336:195-198. References in this figure pertain to references in article cited.)*

exhibited an inverse relationship to thienopyridine treatment efficacy, platelet reactivity was evaluated in consecutive patients (n = 16) undergoing coronary stenting treated with ticlopidine (n = 9) or clopidogrel (n = 7) who experienced subacute stent thrombosis (ST) and compared these with other patients (n = 30; 22 received ticlopidine, 8 received clopidogrel) free of subacute ST. A significant difference in platelet reactivity was noted between these two groups of patients (63.28% ± 9.56% vs. 39.80% ± 10.9%, respectively; $P < .001$).

Matetzky and coworkers[30] evaluated clopidogrel responsiveness in 60 patients with ST-segment elevation MI undergoing primary PCI with stent implantation. The antithrombotic regimen included 300 mg aspirin on admission, heparin, eptifibatide, and clopidogrel 300 mg on completion of PCI and 75 mg daily for 3 months. Patients were stratified into quartiles according to the percentage reduction of ADP (5 µmol/L)-induced platelet aggregation at day 6 compared to baseline and those in the first quartile ($n = 15$) were considered resistant to clopidogrel. At 6-month follow-up, six out of the 15 patients (40%) resistant to clopidogrel developed 7 recurrent ischemic cardiovascular event (acute coronary syndromes [ACS], acute peripheral arterial occlusion, mortality from ischemic stroke), whereas only 1 patient (6.7%) in the second quartile and no patients in quartiles 3 or 4 experienced an event (P for trend = .007) (Fig. 21-8).

The PREPARE POST-STENTING study[31] measured platelet reactivity before hospital discharge by LTA using 20 µmol/L ADP-induced platelet aggregation in 192 patients receiving a clopidogrel loading dose of 300 mg ($n = 75$) or 600 mg ($n = 60$) after nonemergent coronary stenting. Patients with CV death, MI, unstable angina or stroke at 6 months had a higher post-treatment aggregation compared with those without events (63 ± 12% vs. 56 ± 15%; $P = .02$).

In an elective PCI population ($n = 150$), Lev and coworkers[32] determined both aspirin and clopidogrel responsiveness in patients receiving aspirin 81 to 325 mg daily for 1 week or longer while clopidogrel was administered at 300 mg loading dose on completion of the PCI, and 75 mg daily thereafter. Adopting the criteria proposed by Gum[24] and Chen,[25] these investigators defined aspirin resistance as the presence of at least two of the following three: (1) 0.5 mg/mL arachidonic acid-induced platelet aggregation greater than 20%; (2) 5 µmol/L ADP-induced platelet aggregation greater than 70%; and (3) ARU equal to 550 or more by VerifyNow Aspirin. Clopidogrel resistance was defined as baseline minus post-treatment aggregation of 10% or less in response to both 5 and 20 µmol/L ADP. Bivalirudin was used for procedural anticoagulation to reduce the confounding effect of heparin on platelet activation. The incidence of aspirin and clopidogrel resistance was 12.7% and 24%, respectively. Nine (47.4%) of the aspirin-resistant patients were also clopidogrel-resistant. There was a significant increase in the incidence of creatine kinase-MB elevation in aspirin-resistant patients, when compared with aspirin-sensitive patients (38.9% vs. 18.3%; $P = 0.04$). Trends of more frequent creatine kinase-MB elevations were observed in dual drug-resistant and clopidogrel-resistant patients, compared with dual drug-sensitive (44.4% vs. 15.8%; $P = 0.05$) and clopidogrel-sensitive patients (32.4% vs. 17.3%; $P = 0.06$), respectively.

Cuisset and colleagues[33] categorized 106 patients with non-ST–segment elevation (NSTE) ACS undergoing coronary stenting into quartiles according to response to 10 µmol/L ADP-induced platelet aggregation in blood samples drawn before PCI and defined those in the fourth quartile as low responders. These patients received clopidogrel 75 mg daily longer than 5 days ($n = 21$) or a loading dose of 300 mg at least 12 hours before blood sampling ($n = 85$). At 1 month follow-up, CV death, ST, ischemic stroke, or recurrent ACS occurred in 9 patients (39%) in the low-responders versus 3 patients (4%) in the rest with an odds ratio of 22.4 (95% CI 4.6-109). After adjustment for conventional CV risk factors, P-selectin, and C-reactive protein, low-responders had an odds ratio of 41.6 (95% CI 4.74-364) for CV events. The same group of investigators in another study[12] randomized 292 patients with unstable angina/non-ST segment elevation MI undergoing coronary stenting to receive 600-mg or 300-mg

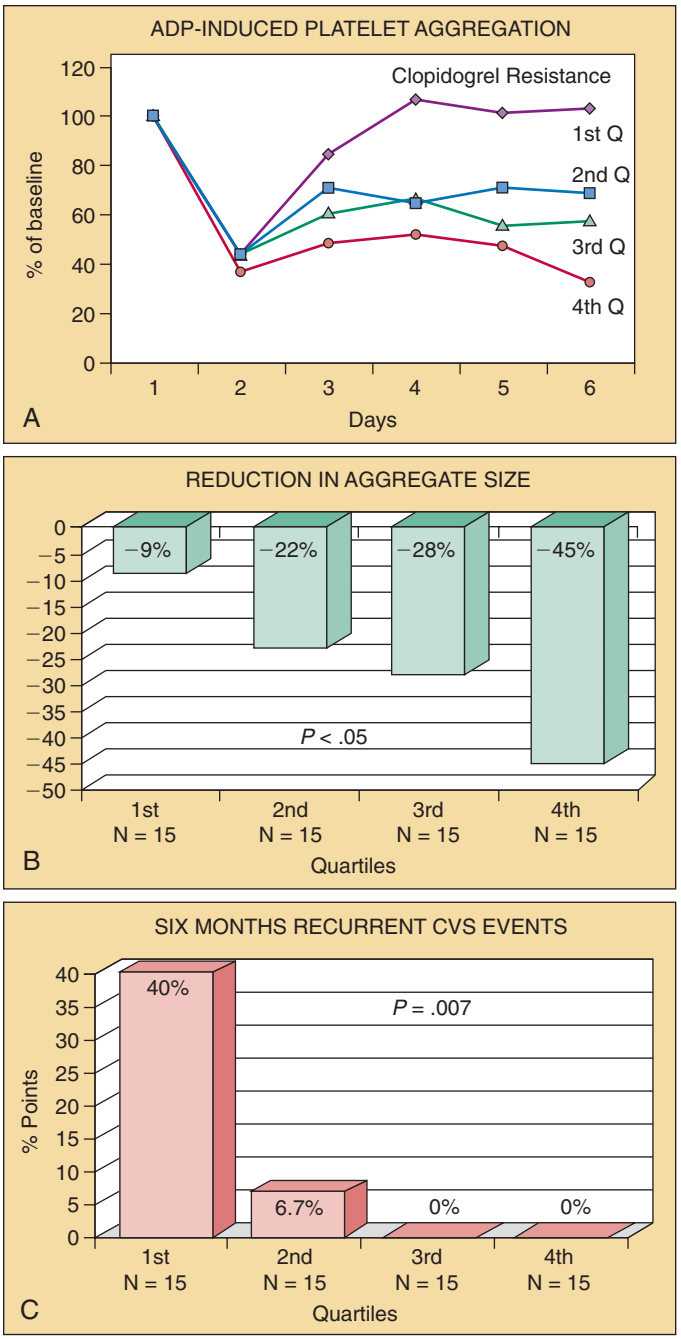

FIGURE 21–8 Study patients were stratified into quartiles according to degree of platelet activity inhibition in response to clopidogrel treatment. Patients in 4 quartiles were compared with regard to (**A**) changes in ADP-induced platelet aggregation expressed as percentage of baseline activity; (**B**) percentage reduction in aggregate size at day 6 compared with baseline values; and (**C**) incidence of recurrent major adverse cardiovascular events during a 6-month follow-up. *(From Matetzky S, Shenkman B, Guetta V, et al: Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171-3175.)*

loading dose of clopidogrel at least 12 hours before PCI. They found that patients receiving a 600-mg loading dose of clopidogrel had a lower 10 μmol/L ADP-induced platelet aggregation (50 ± 19% vs. 61 ± 16%; $P < .0001$) before PCI, lower incidence of high post-treatment platelet reactivity (15% vs. 25%; $P = .04$), and recurrent CV events (defined as CV death, ST, ischemic stroke, or recurrent ACS) at 1 month (5% vs. 12%; $P = .02$) compared with those receiving a 300-mg loading dose. Persistence of high post-treatment platelet reactivity was an independent predictor of CV events (OR 13.82; 95% CI 5.30-36.04; $P < .0001$).

Geisler and coworkers[34] tested responsiveness to a loading dose of 600 mg clopidogrel administered at least 6 hours before in 379 patients undergoing coronary stenting (54% stable angina, 46% ACS) using 10 μmol/L ADP-induced platelet aggregation and used less than 30% platelet inhibition to define a low response to clopidogrel. Low responders (5.8%) had a higher risk of nonfatal MI, nonfatal stroke, or CV death at 3 months (22.7% vs. 5.6%; $P = .004$). Low response to clopidogrel was independently associated with CV events at 3 months on multivariable analysis (HR 3.71; 95% CI 1.08-12.69; $P = .037$).

The EXCELSIOR study[35] evaluated 802 low-risk patients undergoing elective coronary stenting pretreated with 600 mg loading dose of clopidogrel from less than 2 hours to more than 6 hours before PCI. Platelet function was tested immediately before PCI by optical aggregometry using 5 μmol/L ADP-induced platelet aggregation and the responses were divided into quartiles. The incidence of death, MI, and target lesion revascularization (major adverse cardiac events, MACE) was 0.5% in lowest 2 quartiles, 3.1% in the third quartile, and 3.5% in the top quartile ($P = .034$). Platelet aggregation above the median carried a 6.7 fold risk (95% CI 1.04-29.41; $P = .003$) of 30-day MACE. Multivariable analysis revealed platelet aggregation as an independent predictor of 30-day MACE (adjusted OR per 10% increase in platelet aggregation 1.32; 95% CI 1.04-1.61; $P = 0.026$).

The RECLOSE study[36] evaluated 6-month cardiovascular outcomes post-drug eluting stenting (DES) stratified by clopidogrel responsiveness. Nonresponders were defined as greater than 70% aggregation by LTA (10 μM ADP) 12 hours after 600-mg clopidogrel load. The primary end point was the incidence of definite/probable early, subacute, and late stent thrombosis at 6-month follow-up. Stent thrombosis occurred in 3.1% of the overall cohort ($n = 804$). The incidence of stent thrombosis was 8.6% in nonresponders compared with 2.3% in responders ($P < .001$). By multivariate analysis, the predictors of stent thrombosis included nonresponsiveness to clopidogrel (HR 3.08; 95% CI 1.32-7.16; $P = .009$), left ventricular ejection fraction (HR 0.95; 95% CI 0.92-0.98; $P = .001$), total stent length (HR 1.01; 95% CI 1.00-1.02; $P = .010$), and ST-segment elevation acute myocardial infarction (HR 2.41; 95% CI 1.04-5.63; $P = .041$). Thus, nonresponsiveness to clopidogrel is a strong independent predictor of stent thrombosis in patients receiving DES.

Bliden and coworkers[37] studied 100 patients receiving clopidogrel 75 mg daily for 1 month or longer before undergoing nonemergent coronary stenting. Platelet reactivity was assessed by LTA using 5 μmol/L ADP-induced platelet aggregation. High on-treatment platelet reactivity was defined by 50% or greater aggregation and was noted in 22% of the studied population. Ischemic events (CV death, MI, unstable angina, target vessel revascularization [TVR], and non TVR) at 1 year occurred in 23 patients; 70% of these displayed high on-treatment platelet reactivity, whereas only 8% of the patients without an ischemic event displayed high on-treatment platelet reactivity. Multivariable analysis identified high on-treatment platelet reactivity as the only variable associated with ischemic events (OR 34.6; 95% CI 8.3-144.2; $P < .001$).

Cuisset and coworkers[38] enrolled 190 patients with unstable angina/non-ST segment elevation myocardial infarction (NSTEMI) undergoing coronary stenting. A loading dose of 600 mg clopidogrel was administered at least 12 hours before stenting. Blood samples for platelet reactivity were drawn in the catheterization laboratory from arterial sheaths at least 12 hours after the clopidogrel loading dose. Platelet aggregation was assessed using 10 μmol/L ADP stimulation and a response of greater than 70% was considered high post-treatment platelet reactivity, which was present in 22% of the patients. Periprocedural MI, defined by troponin I elevation of greater than 0.4 ng/mL, occurred more frequently in patients with high post-treatment platelet reactivity than those without (43% vs. 24%, OR 2.43; 95% CI 1.18-4.97; $P = .0143$).

Angiolillo and coworkers[39] investigated platelet reactivity in type 2 diabetic patients after coronary stenting. These subjects had received clopidogrel 75 mg and aspirin 100 mg daily for 6 to 9 months post PCI. Platelet function was assayed by LTA using 20 μmol/L ADP-induced aggregation and divided into quartiles. The upper quartile defined high platelet reactivity. Clopidogrel was discontinued 3 to 6 months after platelet function assay. Cardiovascular death, MI or stroke occurred in 37.7% of the patients in the upper quartile compared with 15.2%, 12.2%, and 12.2% in the lower three quartiles ($P = .005$). The strongest predictor of ischemic events was high platelet reactivity by multivariable analysis (HR 3.35; 95% CI 1.68-6.66; $P = .001$). A cutoff value of 62% maximal platelet aggregation was found by receiver-operating characteristic analysis to be the best predictor of ischemic events (37.8% vs. 13.2%; OR 3.96; 95% CI 1.8-8.7; $P < .001$).

The studies discussed so far employed platelet function assays that are time-consuming, technically demanding, and not readily accessible for clinical use. The following three studies tested whether clopidogrel responsiveness measured by point-of-care assays correlated with post-PCI ischemic complications. Price and collegues[9] measured platelet reactivity in 380 patients scheduled for elective drug-eluting stent implantation using the VerifyNow purinergic G protein–coupled P2Y 12 (P2Y12) receptor assay. Blood sample was obtained from the arterial sheath just before PCI in those receiving a maintenance dose of 75 mg daily for more than 5 days. Patients receiving a loading dose of clopidogrel at 600 mg at the conclusion of PCI had phlebotomy for blood sampling 12 hours after PCI. Platelet reactivity was reported in P2Y12 reaction units (PRU). Post-treatment PRU were normally distributed with a mean of 184 ± 85. The combined endpoint of CV death, MI, or ST occurred in 10 patients (2.6%). A PRU of 235 or more (sensitivity 78%; 95% CI 46-94; specificity 68%; 95% CI 67-69; negative predictive value 99%; 95% CI 98-100) was identified as the optimal cutoff value to predict CV events. Patients with post-treatment reactivity greater than the cutoff value had a significantly higher rates of CV death (2.8% vs. 0%; $P = .04$), stent thrombosis (4.6% vs. 0%; $P = .004$), and the combined endpoint (6.5% vs. 1.0%; $P = .008$).

The ARMYDA-PRO study[40] also used the VerifyNow $P2Y_{12}$ assay to test platelet reactivity in the cardiac catheterization laboratory on 160 patients undergoing PCI for NSTE ACS or stable ischemic syndromes. All patients received 600 mg loading dose of clopidogrel about 6 hours before PCI ($n = 120$) or were receiving clopidogrel 75 mg daily for 5 days or more. Cardiac death, MI, and TVR at 30 days occurred more frequently in patients with pre-PCI PRU in the fourth quartile compared with those in the lowest quartile (20% vs. 3%; $P = .034$). Multivariable analysis revealed a significantly increased risk of 30-day cardiac events associated with pre-PCI PRU in the fourth quartile (OR 6.1; 95% CI 1.1-18.3; $P = .033$). A pre-PCI PRU greater than 240, comparable to the one identified by Price and coworkers, was found to be the optimal cutoff for the cardiac events (area under curve

TABLE 21–1 Prospective Studies Relating Clopidogrel Nonresponsiveness to Adverse Clinical Events

Population Studied	Clopidogrel Dose	Definition of Nonresponsiveness	Incidence of Non-responsiveness	Adverse Clinical Events
STEMI patients (n = 60)[26]	LD 300 mg MD 75 mg	LTA (5 µmol/L ADP); first quartile of reduction in aggregate size	25%	40% vs. 6.7% (P for trend=.007) had ACS, acute peripheral arterial occlusion, mortality from ischemic stroke
Patients undergoing non-emergent coronary stenting (n = 192)[27]	LD 300 mg (n = 75), 600 mg (n = 60) MD 75 mg	LTA (20 µmol/L ADP); fourth quartile of aggregation	Not defined	Post-treatment aggregation 63 ± 12% in patients with events (CV death, MI, UA, or stroke at 6 months) vs. 56 ± 15% in patients without events (P=.02)
Patients undergoing elective coronary stenting (n = 150)[28]	LD 300 mg MD 75 mg	LTA (5 and 20 µmol/L ADP); <10% reduction compared with baseline	24%	2.3-fold increased risk of creatine kinase-MB elevation after PCI (P = .06)
Patients undergoing coronary stenting for UA/NSTEMI (n = 106)[29]	LD 300 mg MD 75 mg (n = 85), 75 mg >5 days (n = 21)	LTA (10 µmol/L ADP); fourth quartile of aggregation	22%	22.4-fold increased risk of CV death, stent thrombosis, ischemic stroke, or recurrent ACS at 1 month
Patients undergoing coronary stenting for UA/NSTEMI (n = 292)[34]	LD 300 mg (n = 146), 600 mg (n = 146) MD 75 mg	LTA (10 µmol/L ADP); aggregation >70%	LD 600 mg 15% LD 300 mg 25%	13.8-fold increased risk of CV death, stent thrombosis, ischemic stroke, or recurrent ACS (P = .0001) at 1 month
Symptomatic CAD patients undergoing coronary stenting (n = 379)[30]	LD 600 mg MD 75 mg	LTA (20 µmol/L ADP); aggregation >70%	5.8%	3.7-fold increased risk of CV death, MI, or stroke at 3 months
Patients undergoing elective coronary stenting (n = 802)[31] (EXCELSIOR)	LD 600 mg MD 75 mg	LTA (20 µmol/L ADP); non-responsiveness not defined	Not defined	6.7-fold risk of death, MI, and target lesion revascularization at 30 days for platelet aggregation > median (P = .003)
Patients undergoing non-urgent coronary stenting (n = 100)[33]	75 mg daily ≥1 month	LTA (5 µmol/L ADP) aggregation >50%	22%	35-fold increased risk of CV death, MI, UA, TVR, nonTVR at 12 months
Patients undergoing coronary stenting for UA/NSTEMI (n = 190)[34]	LD 600 mg MD 75 mg	LTA (10 µmol/L ADP); aggregation >70%	22%	2.4-fold increased risk of troponin I elevation after PCI
Type 2 diabetic patients (n = 173) 6-9 months after coronary stenting[35]	75 mg daily for 3-6 months	LTA (20 µmol/L ADP); fourth quartile of aggregation	26%	3.4-fold increased risk of CV death, MI, or stroke at 2 years
Patients undergoing elective coronary stenting (n = 380)[12]	LD 600 mg or 75 mg daily ≥5 days	Point-of-care platelet aggregation assay; PRU ≥235	32%	6.5% vs. 1.0% (P = .008) had CV death, MI, or stent thrombosis at 6 months
Patients undergoing non-urgent coronary stenting (n = 160)[36] (ARMYDA-PRO)	LD 600 mg or 75 mg daily ≥5 days	Point-of-care platelet aggregation assay; PRU in the fourth quartile	25%	6-fold increased risk of cardiac death, MI, or TVR
Patients undergoing urgent and non-urgent coronary stenting (n = 1,608)[37]	LD 600 mg MD 150 mg for 3 days then 75 mg daily	Point-of-care platelet aggregation assay; upper quintile	20% 13%	11-fold increased risk of definite stent thrombosis at 30 days 3.1-fold increased risk
Patients undergoing urgent and non-urgent DES[32] (RECLOSE)	LD 600 mg MD 75 mg	LTA (10 µmol/L ADP) >70% aggregation		Definite/probable stent thrombosis

LD, loading dose; MD, maintenance dose.

0.69; 95% CI 0.56-0.81; P = .016; sensitivity 81%; specificity 53%).

The largest prospective study linking clopidogrel responsiveness to clinical outcomes was reported by Sibbing and coworkers.[41] A total of 1608 patients undergoing drug-eluting stent implantation were enrolled. Both clopidogrel-naïve patients and patients on clopidogrel maintenance therapy received a loading dose of 600 mg clopidogrel 2 hours or less before PCI. Whole blood was obtained from the arterial sheath before PCI. Platelet aggregation was assessed using a point-of-care assay called multiple electrode platelet aggregometry (MEA) and was quantified as Aggregation Unit (AU) and area under the curve of AU (AU·min). A cutoff at the upper quintile defined low response to clopidogrel. Low responders had a significantly higher risk of definite stent thrombosis at 30 days (2.2% vs. 0.2%; OR 9.4; 95% CI 3.1-28.4; P < .0001) and the composite of death or definite stent thrombosis (3.1% vs. 0.6%; OR 5.1; 95% CI 2.2-11.6; P < .001). An optimal cutoff value for predicting stent thrombosis of 468 AU·min was identified, with 70% sensitivity, 84% specificity, and an area under curve of 0.78 (95% CI 0.60-0.96; P = .001).

Thus, multiple trials have demonstrated the clinical implications of clopidogrel responsiveness in patients undergoing PCI and are summarized in Table 21-1. A systematic review

and meta-analysis of clopidogrel nonresponsiveness and cardiovascular outcomes in patients undergoing PCI with stenting has been reported.[2] Twenty five studies that included a total of 3688 subjects were evaluated. Patients with cardiovascular disease and treated with 75 to 325 mg of aspirin were included. Compliance was confirmed directly in only 14 studies and the mean prevalence of clopidogrel nonresponsiveness was 21% (95% CI 17%-25%). The pooled odds ratio of major adverse cardiovascular events in clopidogrel nonresponders compared with responders was 8.0 (95% CI 3.4-19.0).

STRATEGIES TO OVERCOME NONRESPONSIVENESS

The clinical usefulness of adjusting therapy according to clopidogrel responsiveness was investigated by Bonello and coworkers[42] in a multicenter prospective randomized study. A total of 162 patients undergoing PCI for stable angina or unstable angina/NSTEMI with a VASP greater than 50% 24 hours after a 600 mg dose of clopidogrel were randomized to the control group or to the VASP-guided group. In the latter group, up to 3 additional boluses of 600 mg of clopidogrel could be given in 24-hour increments and the VASP index was determined 12 hours after administration until a VASP index greater than 50% was obtained. If the VASP index could not be reduced to less than 50%, PCI was performed without further loading doses. Out of 78 patients in the VASP-guided group, 11 patients (14%) could not have the VASP decreased to less than 50% after the fourth loading dose. The occurrence at 1 month of CV death, angiographically confirmed ST, recurrent ACS, and recurrent revascularization was noted in eight patients (10%) in the control group compared with none in the VASP-guided group ($P = .007$). The rate of bleeding was not statistically different between the two groups (5% vs. 4%, $P = 1$). The same group of investigators conducted a similar study[43] with a larger sample size ($N = 429$). The VASP-guided group had a significantly lower rate of definite ST at 30 days (0.5% vs. 4.2%, $P < .01$), lower rate of major CV events (0.5% vs. 8.9%, $P < .01$), and similar rate of bleeding (3.7% vs. 2.8%, $P = .8$).

The use of alternative antiplatelet agents may be an option for managing antiplatelet nonresponsiveness. Prasugrel, a third-generation thienopyridine, has been shown to give higher and more consistent levels of active metabolite after hepatic cytochrome-dependent conversion. Higher levels of platelet inhibition are achieved with lower interpatient variability and fewer patients displaying nonresponsiveness.[44,45] Indeed, when compared with approved doses of clopidogrel (300 mg loading dose and 75 mg maintenance dose), prasugrel (60 mg loading dose and 10 mg maintenance dose) was associated with lowered rates of ischemic events (cardiovascular death, nonfatal MI, or nonfatal stroke: 9.9% in prasugrel group vs. 12.1% in clopidogrel group; HR 0.81; 95% CI 0.73-0.90; $P < .001$), but at the expense of increased major bleeding (prasugrel 2.4% vs. clopidogrel 1.8%; HR 1.32; 95% CI 1.03-1.68; $P = .03$) in patients with ACS undergoing PCI.[46] Additional P2Y12 receptor antagonists, such as ticagrelor, and elinogrel, also have enhanced potency (with the potential for greater than 80% inhibition of platelet aggregation), more rapid onset (seconds to about 60 min) and markedly reduced response variability. They are currently being evaluated in phase II/III clinical trials.

SUMMARY

Numerous studies have documented interindividual variability in platelet inhibitory responsiveness to oral antiplatelet drugs. There is considerable emerging evidence demonstrating that hyporesponsiveness or nonresponsiveness to antiplatelet drugs in the laboratory (i.e., resistance) is associated with adverse clinical events in diverse populations of patients with atherosclerotic disease in stable or unstable phase, or in the setting of percutaneous coronary and peripheral interventions. However, there are major limitations of the currently available data. The number of patients studied in all these reports is relatively small. The study designs are not adequate for controlling confounding variables. The definitions of antiplatelet resistance are not uniform. In studies of aspirin, aspirin dosage varies and treatment compliance is not verified. Widespread clinical application of platelet function testing for the determination of antiplatelet resistance will require additional studies on larger populations that define antiplatelet resistance in a standardized manner using assays with consistency and reproducibility, that correlate the measurements with clinical outcomes, and that provide strategies for modifying antiplatelet regimens to improve outcome (e.g., increasing dose of antiplatelet agent, adding or substituting second antiplatelet agent). Laboratory platelet function testing is likely to be complemented by genetic testing based on the emerging genetic studies[10-13] demonstrating that patients with loss-of-function genetic polymorphisms have altered pharmacokinetic and pharmacodynamic responses to clopidogrel and an increased risk for recurrent cardiovascular events, especially for carriers of the CYP2C19*2 allele, who had a 3-fold increased risk of stent thrombosis compared with noncarriers.

We have seen two small studies in which tailoring clopidogrel loading doses according to platelet function testing led to improvement in clinical outcomes after PCI. The efficacy and safety of increasing the daily dose of clopidogrel (75 vs. 150 mg daily) will be tested definitively in the multi-center, double-blind, randomized GRAVITAS trial.[47] In the case of aspirin nonresponsiveness, the ASCET study is recruiting stable patients with angiographically documented coronary artery disease to evaluate whether switching to clopidogrel will be superior to continued aspirin therapy in improving clinical outcomes among aspirin-resistant patients.[48] Routine monitoring of antiplatelet therapy based on guideline recommendations will require completion of studies such as GRAVITAS, ASCET, and others. It seems reasonable that just as anti-hypertensive, anti-hyperlipidemia, and anticoagulant agents are dosed in response to blood pressure, lipid, and coagulation responses, respectively, ex vivo measures of platelet inhibitory responses will likely play an integral role in the management of patients with cardiovascular disease.

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CHAPTER 22

Anticoagulants

Shannon M. Bates and Jeffrey I. Weitz

THE ROLE OF THROMBOSIS IN ISCHEMIC HEART DISEASE

Although acute coronary syndromes are divided for the purpose of treatment assignment into unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), the clinical manifestations in all three instances usually are triggered by disruption of atherosclerotic plaque and the development of superimposed thrombus.[1-3] Arterial thrombi, which form under high shear conditions, consist of platelet aggregates held together by small amounts of fibrin.[4] After plaque disruption, platelets adhere to newly-exposed subendothelial matrix components, particularly collagen and von Willebrand factor, via constitutively expressed receptors (Fig. 22-1). Adherent platelets become activated and recruit additional platelets by synthesizing thromboxane A_2 and releasing adenosine diphosphate (ADP). Platelet activation induces conformational changes in glycoprotein (GP) IIb/IIIa, one of the most abundant receptors on the platelet surface. By binding fibrinogen or, under high shear conditions, von Willebrand factor, conformationally activated GP IIb/IIIa cross-links adjacent platelets,[5] resulting in platelet aggregation.

Damage to the vascular wall also exposes tissue factor (TF)-expressing cells to blood.[5] Lipid-laden macrophages in the core of atherosclerotic plaques are particularly rich in TF,[3] thereby explaining the propensity for thrombus formation at sites of plaque disruption. Exposed TF binds activated factor VII, which is found in small amounts in plasma as well as factor VII. Once bound to TF, factor VII can undergo autoactivation, thereby augmenting the local concentration of factor VIIa.[6]

The factor VIIa/TF complex, also known as extrinsic tenase, activates factors IX and X, leading to the generation of factors IXa and Xa, respectively. Factor IXa binds to factor VIIIa on the surface of activated platelets to form intrinsic tenase, a complex that also activates factor X. Factor Xa, generated through the extrinsic and intrinsic tenase complexes, assembles on the surface of activated platelets as part of the prothrombinase complex (factor Xa, factor Va, and calcium) that converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin, and activates factor XIII, which by cross-linking the fibrin network, stabilizes the platelet/fibrin thrombus. Thrombin also triggers thrombus growth via several mechanisms. It amplifies its own generation by feedback activation of factors V and VIII and it also serves as a potent platelet agonist.[5] The resultant intraluminal thrombus superimposed on disrupted atherosclerotic plaque impairs blood flow.

Because arterial thrombosis involves activation of coagulation in addition to platelet aggregation, most current strategies for its prevention and treatment focus on both attenuating thrombin generation and inhibiting platelet aggregation. Coronary arteries occluded by thrombus can have blood flow restored by mechanical or pharmacologic means. Mechanical reperfusion is effected by balloon angioplasty with or without coronary stent insertion, whereas pharmacologic reperfusion therapy involves the administration of fibrinolytic drugs to degrade the fibrin component of the coronary thrombus.

Antithrombotic therapy is a mainstay of treatment of acute coronary syndromes. Antithrombotic drugs fall into three categories: antiplatelet agents, anticoagulants, and fibrinolytic drugs (Fig. 22-2). Antiplatelet agents inhibit platelet activation and/or aggregation, whereas anticoagulants target one or more of the clotting factors, thereby attenuating fibrin formation. As indicated earlier, fibrinolytic drugs are administered to degrade fibrin.

This chapter focuses on anticoagulants. Currently available anticoagulants include parenteral agents and orally active drugs. The parenteral agents are unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux. Although LMWH and fondaparinux represent advances over UFH, they still must be administered parenterally. The only orally available anticoagulants licensed for long-term use are the vitamin K antagonists. Although effective, these drugs have a narrow therapeutic window and an

COORDINATED ROLE OF PLATELETS AND THE COAGULATION SYSTEM IN THROMBOGENESIS

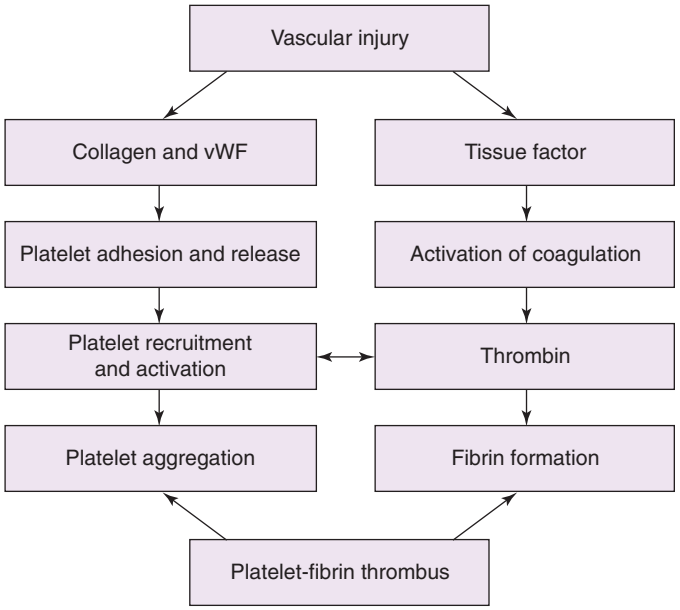

FIGURE 22–1 Coordinated role of platelets and the coagulation system in thrombogenesis. Vascular injury simultaneously triggers platelet activation and aggregation, and activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (vWF) onto which platelets adhere. Adherent platelets become activated and release adenosine diphosphate (ADP) and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. When platelets are activated, glycoprotein IIb/IIIa on their surfaces undergoes a conformational change that enables it to ligate fibrinogen and mediate platelet aggregation. Coagulation is triggered by tissue factor exposed at the site of injury. Tissue factor triggers thrombin generation. As a potent platelet agonist, thrombin amplifies platelet recruitment to the site of injury. Thrombin also converts fibrinogen to fibrin and the fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus.

SITES OF ACTION OF ANTICOAGULANT AGENTS

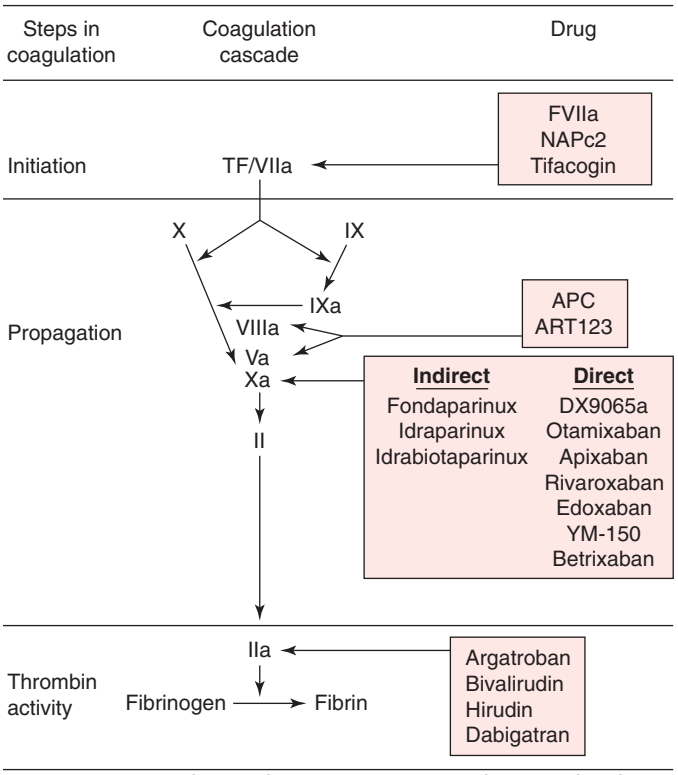

FIGURE 22–3 Sites of action of anticoagulant agents. The formation of the factor VII/tissue factor complex (VIIa/TF) triggers coagulation. This complex activates factors IX and X. The activated form of factor IX (factor IXa), in concert with its activated cofactor, factor VIIIa, propagates coagulation by activating factor X. Activated factor X (factor Xa), with its cofactor, activated factor V (factor Va), converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin. As indicated, the various anticoagulants target different steps in these pathways.

unpredictable dose response, necessitating frequent monitoring to ensure that a therapeutic effect is achieved. Focusing on anticoagulants used in the management of acute coronary syndromes, their mechanisms of action and recent clinical trial data supporting their use will be reviewed. Particular attention will be paid to more recently developed anticoagulants and the opportunities presented by these agents.

ANTICOAGULANTS

Currently available anticoagulants include both parenteral and oral agents. Rapidly acting parenteral agents are typically used for the initial treatment of arterial thromboembolism, whereas oral agents are used for long-term therapy. Anticoagulants can inhibit initiation or propagation of coagulation. Agents that target the factor VIIa/TF complex block the initiation of coagulation, whereas propagation of coagulation can be blocked by drugs that target factors IXa or Xa, or by inactivation of factors Va or VIIIa, key cofactors in coagulation. Thrombin inhibitors prevent fibrin formation, block thrombin-mediated feedback activation of factors V and VIII, and attenuate thrombin-induced platelet aggregation (Fig. 22-3).

CLASSIFICATION OF ANTITHROMBOTIC DRUGS

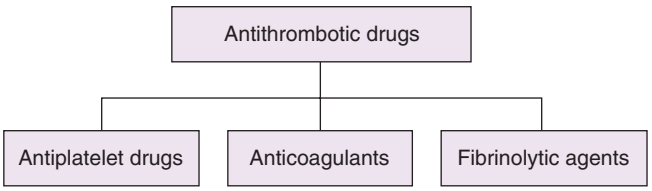

FIGURE 22–2 Classification of antithrombotic drugs.

THROMBIN INHIBITORS

The procoagulant effects of thrombin can be blocked either by inactivating the enzyme itself or by preventing its generation from precursor coagulation proteins. Indirect thrombin inhibitors such as UFH and LMWH activate the naturally occurring thrombin inhibitor, antithrombin. Direct thrombin inhibitors act in an antithrombin-independent manner by binding directly to thrombin and blocking its interaction with its substrates. The most extensively studied direct thrombin inhibitors are hirudin and bivalirudin.

INDIRECT THROMBIN INHIBITORS

Unfractionated Heparin

Mechanism of Action

Unfractionated heparin acts as an anticoagulant by activating antithrombin.[7] A pentasaccharide sequence, randomly

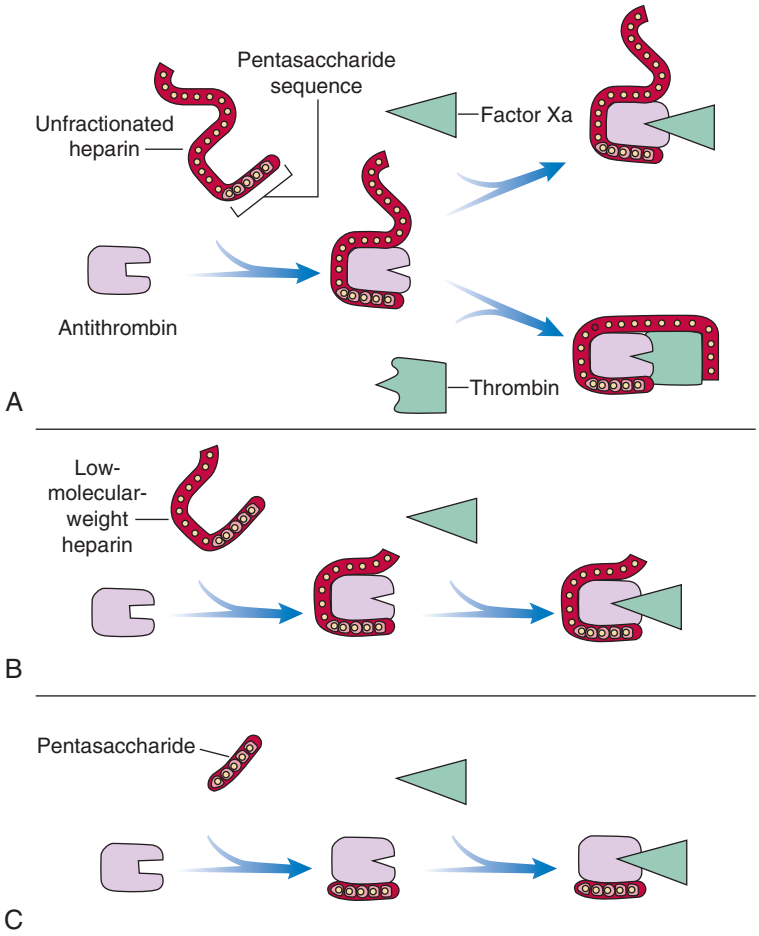

FIGURE 22–4 Mechanism of action of heparin, low-molecular-weight heparin and fondaparinux, a synthetic pentasaccharide. **A,** Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which corresponds to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. **B,** Low-molecular-weight heparin (LMWH) has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500 to 5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. **C,** The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

distributed along one third of the heparin chains, mediates the interaction between heparin and antithrombin (Fig. 22-4). Upon binding, heparin induces a conformational change in the reactive site loop of antithrombin that changes it from a slow thrombin and factor Xa inhibitor to a very rapid inhibitor of these coagulation enzymes. To enhance thrombin inhibition by antithrombin, heparin must bind simultaneously to the enzyme and the inhibitor, thereby promoting formation of a ternary thrombin/antithrombin/heparin complex.[8,9] Only pentasaccharide-containing chains that contain at least 13 additional saccharide units and have a molecular mass of 5400 or greater are of sufficient length to perform this bridging reaction. In contrast, because bridging is unnecessary to enhance the inactivation of factor Xa by antithrombin, pentasaccharide-containing chains of any length will catalyze this reaction.

Indications

Acute Myocardial Infarction with Thrombolysis. The role of subcutaneous UFH after thrombolysis in aspirin-treated patients has been examined in three large multicenter randomized trials.[10-12] Together, these studies indicate that high-dose subcutaneous UFH (12,500 units twice daily, beginning 4 to 12 hours after initiation of thrombolytic therapy) produces no statistically significant reduction in long-term mortality, although there may be a reduction in deaths during the treatment period. Moreover, UFH produces a small, but statistically significant, increase in major bleeds. The substitution of intravenous heparin for subcutaneous heparin provides no advantage in terms of reducing mortality and nonfatal stroke in patients receiving streptokinase.[12] Based primarily on the data suggesting an early mortality benefit, the American College of Chest Physicians Consensus Guidelines provides a weak recommendation for the use of intravenous UFH in patients receiving streptokinase.[13]

The results of small patency trials[14-16] and the first GUSTO trial[17] have been invoked to support the routine early administration of intravenous UFH in patients given other lytic agents (e.g., alteplase, anistreplase, reteplase, or tenecteplase). It is recommended that such patients be treated with heparin for 48 hours. Continuation beyond this time should be considered only in patients at high risk of systemic or venous thromboembolism.[13] More recent meta-analyses have shown no net mortality benefit associated with intravenous UFH when used in conjunction with thrombolytics and full-dose aspirin.[18,19] Additionally, the early termination of both the TIMI-9A[20] and GUSTO IIa[21] trials because of excessive major bleeding in patients receiving intravenous UFH (despite the

fact that the heparin dose used was only 20% higher than that used in previous trials), emphasizes the potential hazards of high-dose UFH in this setting. This concern is reflected in subsequent recommendations to use a weight-based dosing nomogram with a reduced intensity of UFH treatment in patients receiving thrombolytic therapy.[13,22]

Unless a specific contraindication exists, patients undergoing coronary thrombolysis who do not receive high-dose UFH should be given thromboprophylaxis with low-dose heparin therapy until ambulatory.[13]

Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction. There is considerable confusion and controversy regarding recommendations for the use of UFH in patients with unstable angina or NSTEMI. Interpretation of data is difficult because of variations in regimens, patient population heterogeneity, and small trial size. A number of small trials have shown limited benefit when heparin is added to aspirin in these patients.[23-25] A meta-analysis of these trials demonstrated a 33% reduction in the relative risk of MI or death with the addition of intravenous UFH to aspirin in patients with unstable angina.[26] Although this difference was not statistically significant, it suggests there may be a benefit. Current practice guidelines, therefore, support the use of intravenous UFH in addition to aspirin for treatment of unstable angina.[27]

Percutaneous Coronary Interventions. Intravenous UFH has been used since the advent of percutaneous coronary interventions to prevent arterial thrombus formation at the site of arterial injury and to reduce the thrombogenicity of catheter equipment and guide wires used during the procedure.[28,29] There is no evidence to support the routine use of postprocedural heparin in patients undergoing uncomplicated coronary angioplasty.[30,31]

Limitations of Unfractionated Heparin

The discontinuation of UFH treatment in patients with unstable angina or NSTEMI is associated with a clustering of recurrent ischemic events[32,33] and abrupt vessel closure after successful coronary angioplasty occurs in up to 10% of patients, despite the use of high-dose heparin in addition to aspirin.[28] This reactivation of the thrombotic process after heparin discontinuation has been attributed, at least in part, to the inability of the heparin/antithrombin complex to inactivate thrombin bound to fibrin,[34,35] fibrin degradation products,[34] and activated factor X (factor Xa) bound to activated platelets trapped within the thrombus.[36,37] By activating prothrombin, bound factor Xa increases the amount of thrombin available to bind to fibrin.[36] Because thrombin bound to fibrin remains enzymatically active and protected from inactivation,[34] it can trigger thrombus growth by locally activating platelets[38] and amplifying coagulation.[39]

Nonspecific binding of UFH to endothelial cells, plasma proteins, or proteins released from activated platelets at the site of plaque rupture[40-42] results in reduced bioavailability, a dose-dependent half-life, and an unpredictable anticoagulant response.[43] This necessitates careful laboratory monitoring when UFH is given in therapeutic doses.

Advantages of Unfractionated Heparin

UFH does have advantages over other anticoagulants. First, its anticoagulant effects can be rapidly and completely neutralized by protamine sulfate, a useful characteristic if bleeding occurs or urgent cardiopulmonary bypass is required. Second, UFH is not cleared by the kidneys and, therefore, can be used in patients with renal insufficiency.

Dosages

Because the anticoagulant response to UFH varies among patients, laboratory monitoring is essential to ensure that adequate anticoagulation is achieved. UFH is usually monitored using the activated partial thromboplastin time (aPTT).[44] The therapeutic aPTT range, which targets a minimum and a maximum anticoagulant effect, differs depending on the aPTT reagent and coagulometer used to perform the test.[45] Several studies have demonstrated that the use of a nomogram to adjust heparin doses improves the likelihood of obtaining a therapeutic effect.[44,46]

In general, the doses of heparin recommended for treatment of acute coronary syndromes are lower than those to treat venous thromboembolism. Although it is accepted that the therapeutic aPTT range for treatment of venous thromboembolism corresponds to a heparin level of 0.3 to 0.7 anti-Xa units/mL (0.2 to 0.4 units/mL by protamine titration),[47] the therapeutic range for coronary indications is unknown, but is likely to correspond to heparin levels that are about 10% lower than those needed to treat patients with venous thromboembolism. In patients with unstable angina or NSTEMI, the American College of Cardiology recommends that intravenous UFH be initiated with a bolus of 60 to 70 units/kg to a maximum of 5000 units, followed by an initial maintenance dose of 12 to 15 units/kg/hour (maximum of 1000 units/hour).[22,27] Patients with acute MI treated with thrombolytics should receive even lower doses. Here the recommended bolus of UFH is 60 units/kg to a maximum dose of 4000 units at the initiation of thrombolysis, followed by an initial maintenance infusion of 12 units/kg/hour, to a maximum dose of 1000 units.[13,48] It is suggested that UFH be continued for 48 hours post thrombolysis. Prophylactic doses of heparin range from 5000 to 7500 units subcutaneously twice daily.[13]

Percutaneous Coronary Interventions

Monitoring of heparin anticoagulation in patients undergoing percutaneous coronary interventions is performed using the activated clotting time (ACT), rather than the aPTT because of the need for point-of-care results and because the large doses of heparin used in these settings produce immeasurably high aPTT results. Patients undergoing percutaneous coronary angioplasty (PTCA) or stent placement without concomitant use of GP IIb/IIIa antagonists should receive a heparin bolus of 60 to 100 units/kg prior to procedure. Incremental boluses should be given to maintain the ACT at 250 to 350 seconds during procedure. The sheath should be removed 4 to 6 hours after an uncomplicated PTCA. Continuation of heparin therapy depends on whether a thrombus or large vessel wall dissection is detected at the end of the procedure. In patients receiving concomitant GP IIb/IIIa antagonists, the heparin bolus should be reduced to 50 to 70 units/kg and incremental boluses given to maintain the ACT between 200 and 250 seconds.[28]

Side Effects

The major complication of UFH is hemorrhage. The absolute risk of hemorrhage depends on the total dose of heparin, the patient's age, the tendency for bleeding, and the concomitant use of thrombolytic drugs, antiplatelet agents, and oral anticoagulants.[49] The risk of major hemorrhage ranges from 1% to 5% when heparin is added to aspirin in low-risk patients, and is as high as 19% in heparin-treated patients receiving concomitant thrombolytic therapy.[50]

Another complication is heparin-induced thrombocytopenia (HIT), which usually develops between 5 and 15 days after heparin is initiated, although it can occur within hours in patients previously exposed to heparin.[51] Arterial or venous thrombosis has been estimated to occur in up to 50% of patients with this syndrome. Venous thrombosis is more common, but arterial thrombosis that includes MI, ischemic stroke, or limb ischemia can occur in patients with HIT.

HIT is initiated when heparin binds to platelets, causing platelet activation[52] and release of platelet factor 4. Heparin

BOX 22-1 Contraindications to Anticoagulant Therapy

Absolute
- Active bleeding
- Severe bleeding diathesis
- Severe thrombocytopenia
- Recent neurosurgery, ocular surgery (excluding cataract surgery), or intracranial bleed

Relative
- Moderate thrombocytopenia
- Bleeding diathesis
- Brain metastases
- Recent major trauma
- Recent major abdominal surgery (<1 or 2 days)
- Gastrointestinal or genitourinary bleeding within the past 14 days
- Endocarditis
- Severe hypertension
- Systolic blood pressure > 200 mm Hg and/or diastolic blood pressure > 120 mm Hg at presentation

binds to platelet factor 4, alters its conformation, and induces the formation of antibodies against the heparin/platelet factor 4 complex.[53,54] Simultaneous binding of these antibodies, usually of the IgG type, to the heparin/platelet factor 4 complex and to platelet Fc receptors causes platelet activation. Thrombosis is thought to be triggered by immune complex-mediated platelet activation, which causes platelet microparticle formation. By serving as a phospholipid surface on which clotting factors assemble, these microparticles can promote thrombin generation,[55] thereby triggering thrombosis.

When given for longer than 1 month, heparin may cause osteoporosis.[43,56] Allergic reactions,[57] alopecia, skin necrosis,[58] and hypoaldosteronism[59] are rare complications of UFH therapy.

Contraindications and Drug Interactions

Therapeutic doses of UFH should not be given to patients who are actively bleeding or who are at high risk of life-threatening bleeding diatheses (Box 22-1). UFH should not be given to patients with a history of HIT.

Concomitant use of oral anticoagulants, antiplatelet agents, fibrinolytic drugs, and GP IIb/IIIa receptor antagonists increases the risk of hemorrhage.[13,49]

Low-Molecular-Weight Heparin

Mechanism of Action

Low-molecular-weight heparins (LMWHs), which have replaced UFH for most indications, are fragments of UFH produced by chemical or enzymatic depolymerization processes that yield glycosaminoglycan chains with a mean molecular mass of approximately 5000 daltons.[60] Like UFH, LMWHs act as anticoagulants by activating antithrombin via a pentasaccharide sequence found on about 20% of these smaller heparin chains (see Fig. 22-4).[7] LMWH exhibits less activity against thrombin than against factor Xa because less than half of the heparin chains are long enough to bridge antithrombin to thrombin.[8,61] Since heparin catalysis of factor Xa inhibition by antithrombin does not require bridging between factor Xa and antithrombin, the smaller pentasaccharide-containing chains in LMWH retain their ability to catalyze factor Xa inhibition.

TABLE 22–1 Advantages of Low-Molecular-Weight Heparin over Unfractionated Heparin

Advantage	Effect	Clinical Consequence
Better bioavailability	Higher drug levels achieved after subcutaneous injection	Subcutaneous administration for prophylaxis or treatment
Reduced binding to proteins	More predictable anticoagulant response	Routine monitoring is unnecessary
Reduced binding to and clearance by endothelial cells and macrophages	Clearance predominantly by renal mechanisms	Longer plasma half-life permits once-daily dosing
Reduced binding to osteoblasts	Reduced activation of osteoclasts	Lower incidence of osteopenia and less risk of heparin-associated osteoporosis and fracture with prolonged treatment
Reduced affinity for platelets and platelet factor 4	Less platelet activation with reduced release of platelet factor 4; reduced formation of complexes of heparin/platelet factor 4	Reduced incidence of heparin-induced thrombocytopenia

Because binding to endothelial cells and to plasma proteins is chain-length dependent, with longer heparin chains having higher affinity than shorter chains, LMWHs bind less avidly to plasma proteins[62,63] and the endothelium[64] than UFH. Consequently, LMWHs produce a more predictable dose-response[65,66] than UFH, and have a longer half-life. With these pharmacokinetic advantages, routine coagulation monitoring of LMWHs is unnecessary. The advantages of LMWH over UFH are summarized in Table 22-1. Because LMWHs are cleared principally by the kidneys and their biologic half-life is prolonged in patients with renal failure,[67] monitoring is necessary when therapeutic doses are given to patients with renal insufficiency.[67] In these individuals, the dose of LMWH should be adjusted to achieve a peak anti-factor Xa heparin concentration of 0.5 to 1.2 units/mL, depending on whether once or twice daily dosing is used and on the type of LMWH utilized. Monitoring may also be advisable in obese patients, although weight adjusted dosing usually results in therapeutic anti-factor Xa levels.

Indications

Myocardial Infarction with Thrombolysis. There is limited experience with LMWH in STEMI. When compared with placebo in patients receiving thrombolysis in four small trials, LMWH reduced reinfarction but was associated with an increased risk of major bleeding, including intracranial hemorrhage.[68-71] In the CREATE trial in which 15,570 patients with ST-segment elevation or new left bundle branch block presenting within 12 hours of symptom onset were randomized to weight-adjusted reviparin or placebo, in addition to usual treatment with fibrinolysis and antiplatelet therapy, treatment with LMWH was associated with a reduction in the primary composite outcome of death, myocardial reinfarction, or stroke at 7 days.[72] Again, there was a small but significant excess of hemorrhagic strokes, as well as an increase in the frequency of life-threatening or major bleeding in patients randomized to reviparin. However, overall, the net clinical benefit (composite outcome of death, MI, stroke, and life-threatening hemorrhage at 7 days) remained in favor of reviparin.[72]

A number of small to moderate-sized trials have compared enoxaparin with UFH as an adjunct to thrombolysis[73-77] and in STEMI patients ineligible for thrombolysis.[78] Overall, enoxaparin therapy was associated with a reduction in reinfarction but an increase in major bleeds, with no overall reduction in mortality.[79] Major bleeding was observed more frequently in patients older than 75 years of age.[74] It has been hypothesized that this was the result of the initial use of a non-weight adjusted intravenous bolus of enoxaparin and the failure to modify enoxaparin dosing according to renal function. Consequently, in the ExTRACT TIMI 25 trial that compared enoxaparin for a median of 7 days with UFH for a median of 2 days in patients receiving fibrinolysis for STEMI,[80] the initial 30-mg intravenous enoxaparin bolus was eliminated and the dose of enoxaparin was adjusted from 1 mg/kg subcutaneously every 12 hours (to a maximum of 100 mg) to 0.75 mg/kg subcutaneously every 12 hours (to a maximum of 75 mg) in patients older than 75 years of age. Additional dose adjustments were made for elevations in baseline creatinine levels. The primary efficacy outcome of all-cause mortality and nonfatal reinfarction at 30 days was significantly lower in the enoxaparin arm than in those receiving UFH. The benefit of enoxaparin was also evident at 48 hours, when both treatments were active. Again there was a significant increase in major and minor bleeds at 30 days in the enoxaparin-treated patients. However, there was no significant difference in the frequency of intracranial hemorrhages between the enoxaparin and UFH-treated groups, and the net clinical benefit (30-day mortality, nonfatal MI, or major bleeding) remained in favor of enoxaparin.

Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction. A number of randomized trials have examined the role of LMWH in aspirin-treated patients with non–ST-segment elevation acute coronary syndromes.[81-86] When added to aspirin in the acute setting, dalteparin is superior to placebo,[81] but similar to UFH, for prevention of death and MI.[82] In contrast, a brief course of therapy with enoxaparin results in a reduction in the risk of death, MI, and recurrent angina compared with UFH; this reduction is sustained for at least 1 year.[83,85,87] Another LMWH, nadroparin, has not been shown to be more effective than UFH in patients with unstable angina or NSTEMI.[85]

The reason for the difference between the results of studies using dalteparin[82] and nadroparin[85] and those using enoxaparin[83,84] is uncertain. Dalteparin and nadroparin are depolymerized by different chemical methods from enoxaparin, and all three LMWHs have different molecular weight distributions. However, these differences are unlikely to explain the more favorable results seen with enoxaparin because a more aggressive LMWH regimen (both in terms of anti-Xa and anti-IIa units) was utilized in the study comparing dalteparin with UFH[82] than in the enoxaparin-containing studies.[83,84] Although the UFH dosage regimens were similar in all of the studies, the average duration of UFH therapy was shorter than that of LMWH therapy in one of the studies evaluating enoxaparin.[84] Additionally, the event rates in patients assigned UFH were higher in the studies evaluating enoxaparin[83,84] than in the trial assessing dalteparin.[82] Although the favorable results with enoxaparin might have been the result of chance, this explanation is less likely given that there are two positive studies with this drug.[83,84] In a single-center open-label randomized comparison of two LMWH preparations in which 438 patients with NSTEMI were randomized to receive 100 units/kg of enoxaparin twice daily or 175 units/kg of tinzaparin once daily for up to 7 days in addition to usual care, enoxaparin was superior to tinzaparin in preventing the primary endpoint (death, MI, refractory angina, or recurrence of unstable angina at day 7).[88,89] The superiority of enoxaparin was maintained through day 30. The superiority of enoxaparin was primarily driven by differences in the rates of recurrent angina at day 7 and day 30, although there was also a difference in the frequency of MI at day 30. The number of hemorrhagic events was similar in the two groups.[88]

Overall, LMWH is associated with at least as favorable outcomes as UFH in this setting. Given these results, the practical convenience of use, and the reduced risk of HIT, LMWHs appear to be a better choice in this setting than UFH.[13]

The prolonged use of LMWH in patients with unstable angina has been examined in four trials.[81,82,84,86] In the first two, prolonged use of a reduced once-daily dose of dalteparin after day 6 did not provide any additional benefit over aspirin.[81,82] Although 3 months of treatment with a higher dose of twice-daily dalteparin significantly reduced the risk of death and MI compared with placebo at 30 days in the FRISC II study, these benefits were not sustained during longer-term follow-up.[86] Similarly, no additional benefit, beyond that seen with in-hospital administration, has been derived from continuing once-daily subcutaneous enoxaparin on an outpatient basis.[84] Given these results, and the increased risk of bleeding complications with extended anticoagulation, the role of outpatient LMWH remains controversial.

The combination of LMWH and GP IIb/IIIa inhibitors has been examined in a number of studies. The results of initial investigations suggested that the combination of LMWH with GP IIb/IIIa inhibitors was likely to be at least as safe and efficacious as UFH plus GP IIb/IIIa antagonists in this patient population.[90-92] These findings were confirmed in a subsequent multicenter open-label noninferiority study of patients with NSTEMI receiving tirofiban in which 2026 participants were randomized to enoxaparin (1 mg/kg subcutaneously every 12 hours) and 1961 received UFH.[93] Enoxaparin was noninferior (but not superior) to UFH with respect to the primary composite endpoint of death, recurrent MI, or refractory ischemia at 7 days. Rates of bleeding were low and similar in both treatment arms.

Percutaneous Coronary Angioplasty. LMWH is replacing heparin for treatment of patients with non–ST-segment elevation acute coronary syndromes, many of whom will require percutaneous coronary interventions, and there is increasing experience with short-term LMWH in place of UFH in this setting. The safety and efficacy of these procedures do not appear diminished by this substitution.[94-98]

Monitoring of LMWH levels during percutaneous coronary interventions is difficult and, consequently, empiric dosing strategies have been developed. In the SYNERGY trial, more than 10,000 high risk non–ST-segment elevation acute coronary artery syndrome patients with planned early invasive intervention were randomized to receive UFH or enoxaparin, in addition to routine medications (including aspirin, clopidogrel, and GP IIb/IIIa antagonists).[98] Enoxaparin was given subcutaneously at a dose of 1 mg/kg every 12 hours. For patients randomly assigned to enoxaparin, cardiac catheterization was performed any time after dosing and the sheath was removed at least 6 to 8 hours after the last LMWH dose. If the last dose of enoxaparin was given less than 8 hours before balloon inflation, no additional LMWH was given during percutaneous coronary intervention. However, if the last dose of enoxaparin was given 8 hours or more before balloon inflation, 0.3 mg/kg of enoxaparin was given intravenously before proceeding with intervention. If intravenous enoxaparin was used, the sheath could be removed at least 4 to 6 hours after the additional dose. Dosing of UFH was according to established guidelines. Enoxaparin was noninferior (but not superior) to UFH with respect to the primary efficacy outcome of all-cause death or nonfatal MI during the first 30 days after randomization. However, there was a modest excess of major (but not severe) bleeding with the enoxaparin strategy.

Short-term administration of LMWH after percutaneous intervention does not appear to reduce the occurrence of early ischemic events[99] or restenosis[100-103] and, therefore, the extended use of LMWH cannot be recommended for this purpose.

Dosages

In general, when given in treatment doses, LMWH can be given once- or twice-daily subcutaneously in weight-adjusted doses without laboratory monitoring.[104] However, for most available LMWHs, only twice-daily dosing regimens have been evaluated in patients with acute coronary syndromes. For dalteparin, the recommended dose is 120 anti-Xa units/kg twice daily,[81,86] whereas for enoxaparin it is 100 anti-Xa units/kg (1 mg/kg) twice daily.[83,84] In patients receiving enoxaparin prior to percutaneous intervention, an intravenous bolus of 0.3 mg/kg is suggested if the last enoxaparin dose is administered between 8 and 12 hours before the procedure.[98] For patients with acute STEMI receiving lytic therapy and enoxaparin who are younger than 75 years of age and have normal renal function, an additional initial 30-mg intravenous bolus of enoxaparin is recommended[80]; however, the bolus is eliminated and the enoxaparin dose reduced to 75 unit/kg every 12 hours for those at least 75 years of age. Based on results of the CREATE trial,[72] if reviparin is used in patients with STEMI receiving thrombolysis, recommended every 12 hourly doses are 3436 units for patients less than 50 kg, 5153 units for those 50 to 75 kg, and 6871 units for those greater than 75 kg. Treatment should be continued for 7 days.

Side Effects and Drug Interactions

Based on results of trials comparing LMWH with UFH in patients with non–ST-segment elevation acute coronary syndromes, LMWH does not increase the risk of major bleeding.[81-84] In the TIMI-11A trial, patients receiving more than 1 mg/kg (100 U/kg) of enoxaparin subcutaneously twice daily were more likely to develop major hemorrhage.[105] These findings suggest that 1 mg of enoxaparin subcutaneously twice daily represents the maximum dose that can be safety given in this setting. The use of LMWH in patients receiving lytic therapy has been associated with a small absolute excess of serious bleeding compared with that seen in patients receiving UFH,[72,74,79] especially in those older than 75 years of age or with renal dysfunction.[74]

Protamine sulfate, widely used as an antidote to neutralize the high doses of UFH administered to patients undergoing cardiopulmonary bypass surgery and to antagonize its hemorrhagic side effects, completely blocks the inhibitory effects of LMWH on thrombin. Because only longer LMWH chains bind protamine sulfate, the anti-Xa activity of LMWH is incompletely reversed.[106] Although studies in laboratory animal models suggest that bleeding produced by very high concentrations of LMWH is reduced with protamine sulfate,[107] similar studies in humans are lacking.

There is evidence from a randomized trial that the incidence of heparin-induced IgG formation and of HIT are lower in patients treated with prophylactic doses of LMWH than in those treated with low-dose UFH,[108] possibly because LMWHs cause less platelet activation[52] and release of platelet factor 4, and because the lower affinity of LMWH for platelet factor 4 results in reduced formation of heparin/platelet factor 4 complexes.

Heparin binding to osteoblasts[109] and osteoclast activation are chain length-dependent and in animal models, bone loss is less marked with LMWH than with UFH.[110,111] These laboratory findings are consistent with the results of small randomized studies that showed a lower incidence of bone fracture[112] and decreased bone mineral density[113] in patients assigned to LMWH than in those randomized to UFH. It should be noted, however, that the risk of osteoporosis with long-term LMWH has yet to be established in large studies.

Contraindications

LMWH should not be used in patients who have absolute contraindications to anticoagulant therapy (see Box 22-1). The risk of hemorrhage is increased with concomitant use of oral anticoagulants, antiplatelet agents, or thrombolytic drugs.[49]

Although the incidence of HIT is lower in patients treated with LMWH than in those given UFH,[108] there is a high degree of in vitro cross-reactivity between LMWHs and the antibody that causes HIT.[114] Additionally, the administration of LMWH can be associated with the development of thrombocytopenia, both in previously unexposed individuals and in those with a history of HIT.[115-117] Therefore, LMWH should not be given to patients with established HIT.

It is probably best to avoid LMWHs in patients with significant renal dysfunction (creatinine clearance below 30 mL/minute) because these drugs are cleared via the kidneys.[67,104] Of the various LMWHs, tinzaparin is the least likely to accumulate in patients with renal impairment because it has the highest mean molecular weight and exhibits less renal excretion than the others.

Fondaparinux

This first-generation synthetic pentasaccharide analogue has high affinity for antithrombin.[118,119] Because it is too short to bridge antithrombin to thrombin, fondaparinux enhances the rate of factor Xa inactivation by antithrombin, but has no effect on the rate of thrombin inhibition (see Fig. 22-4). There is minimal nonspecific binding of fondaparinux to plasma proteins other than antithrombin.[120] Fondaparinux exhibits almost complete bioavailability after subcutaneous injection and has a dose-independent elimination half-life of approximately 17 hours.[118] Fondaparinux is not metabolized and clearance is almost exclusively by the kidneys.[119]

Indications

The antithrombotic efficacy of fondaparinux was demonstrated in four phase III trials comparing this agent to LMWH for thromboprophylaxis after surgery for hip fracture or for elective hip or knee arthroplasty.[121-125] The results of the MATISSE DVT[126] and MATISSE PE[127] trials suggest that once-daily weight-based fondaparinux is as effective and safe as LMWH for the initial treatment of deep vein thrombosis and UFH for the acute treatment of pulmonary embolism.

ST-Segment Elevation Acute Myocardial Infarction. In a randomized, open-label, dose-finding trial, coadministration of fondaparinux and alteplase in STEMI produced similar angiographic patency rates at 90 minutes as did treatment with UFH and alteplase.[128] In a subsequent randomized double-blind trial of 12,092 patients with acute STEMI, the addition of fondaparinux to conventional therapy (either placebo or heparin) for up to 8 days significantly reduced the primary endpoint of death or reinfarction at 30 days.[129] However, in patients undergoing primary percutaneous intervention, there was a higher rate of guiding catheter thrombosis and coronary complications with fondaparinux compared with enoxaparin, although the rates of death or MI were the same in the two groups in this patient population. Among the patients who received UFH prior to primary percutaneous coronary intervention, these differences in catheter thrombosis were not as striking. However, the appropriate dosing of UFH in order to not only avoid catheter-related complications, but also bleeding, remains uncertain. Thus, although fondaparinux is recommended for patients with STEMI receiving fibrinolytic therapy, its use is not recommended in patients with STEMI undergoing primary percutaneous intervention.

Non–ST-Segment Elevation Acute Coronary Syndromes. With pilot studies in patients with unstable angina or NSTE ACSs suggesting that fondaparinux may be as effective as enoxaparin or UFH,[130] a large phase III trial was performed in this population, as well. In the OASIS 5 trial, 20,078 patients with unstable angina or NSTE ACS were randomized to either fondaparinux or enoxaparin for 6 days.[131] The number of patients with primary outcome events at 9 days (death, MI, or refractory ischemia) was similar in the two groups. However, there again was an excess of catheter-related thrombosis in fondaparinux-treated patients compared with enoxaparin-treated patients. Catheter thrombosis was largely avoided by the use of UFH during percutaneous catheter intervention. The frequency of major bleeding was substantially lower in those randomized to fondaparinux and the composite of the primary outcome and major bleeding at 9 days also favored fondaparinux over enoxaparin. Fondaparinux also was associated with a statistically significant reduction in the number of deaths at 30 and 180 days. More than 90% of the excess deaths that occurred in patients treated with enoxaparin occurred in those who experienced bleeding. The lower (prophylactic) dose of fondaparinux used in the OASIS 5 and 6 trials, compared with the standard "therapeutic" doses of LMWH, is likely responsible for the reduced bleeding seen in fondaparinux-treated patients in these studies.[129,131]

Percutaneous Coronary Intervention. In the ASPIRE pilot study, patients undergoing elective or urgent percutaneous coronary intervention were randomized to receive UFH or 2.5 or 5 mg of fondaparinux intravenously.[132] There was a trend toward a lower risk of bleeding in patients randomized to fondaparinux. Although there was no difference between the groups with respect to the composite of death, MI, urgent revascularization, or GP IIb/IIIa antagonist bailout, there was an excess of abrupt closure or angiographic thrombus among patients receiving fondaparinux. These results combined with those seen in the OASIS 5 and 6 trials suggest that fondaparinux should not be considered first-line therapy in ACS patients with planned early invasive management.

Dosages

Based on its excellent bioavailability after subcutaneous injection, lack of variability in anticoagulant response and long half-life, fondaparinux can be administered subcutaneously in once-daily fixed doses without routine laboratory monitoring. Fondaparinux is given at a fixed dose of 2.5 mg subcutaneously per day for thromboprophylaxis. For treatment of deep vein thrombosis or pulmonary embolism, the drug is given at a dose of 7.5 mg subcutaneously daily for patients with a body weight of 50 to 100 kg, 5 mg subcutaneously per day for patients weighing less than 50 kg, and 100 mg per day in those weighing more than 100 kg. For patients with acute coronary syndromes, a once-daily fondaparinux dose of 2.5 mg is used.

Fondaparinux has not been monitored in clinical studies and, therefore, routine coagulation monitoring is not recommended. There may be circumstances when it is useful to determine the anticoagulant activity of fondaparinux and this can be measured using anti-Xa assays; however, the therapeutic anti-Xa range for fondaparinux has not been established.

Side Effects and Drug Interactions

Fondaparinux has low affinity for platelet factor 4. Although fondaparinux may induce the formation of IgG antibodies directed against the platelet factor 4/heparin complex, these antibodies rarely trigger HIT.[133] However, a syndrome resembling HIT has been described in a patient who received fondaparinux after bilateral knee replacement.[134]

To date, studies on the effects of fondaparinux on bone metabolism have been limited to in vitro experiments using cultured osteoblasts. In these investigations, fondaparinux has not been shown to affect osteoblastic[135] or osteoclastic activity.[136]

Fondaparinux does not bind to protamine sulfate, the drug widely used as an antidote to UFH. If uncontrollable bleeding occurs, recombinant factor VIIa may be effective.[137]

Contraindications

Fondaparinux should not be used in patients who have absolute contraindications to anticoagulant therapy (see Box 22-1). The risk of hemorrhage is increased with concomitant use of oral anticoagulants, antiplatelet agents, or thrombolytic drugs.[49] It is best to avoid fondaparinux in patients with significant renal dysfunction (creatinine clearance below 30 mL/minute) because fondaparinux is cleared via the kidneys. Although no placental passage of fondaparinux was demonstrated in an in vitro human cotyledon model,[138] anti-factor Xa activity (at approximately one-tenth the concentration of maternal plasma) was found in the umbilical cord plasma in newborns of five mothers treated with fondaparinux.[139] Although there have been reports of the successful use of this agent in pregnant women,[140,141] the quality of evidence supporting or recommending against the use of fondaparinux during pregnancy is weak and potential deleterious effects on the fetus cannot be excluded.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors bind thrombin and block its interaction with substrates, thus preventing fibrin formation, thrombin-mediated activation of clotting factors V, VIII, or XIII, and thrombin-induced platelet aggregation. As a class, these agents have potential biologic and pharmacokinetic advantages over heparin. Unlike UFH and LMWH, direct thrombin inhibitors inactivate fibrin-bound thrombin,[34] in addition to fluid-phase thrombin. Consequently, direct thrombin inhibitors may attenuate thrombus accretion more effectively. In addition, direct thrombin inhibitors also produce a more predictable anticoagulant effect than UFH because they do not bind to plasma proteins and are not neutralized by platelet factor 4.[142,143]

In vitro and in vivo studies have suggested that direct thrombin inhibitors are more potent antithrombotic agents than UFH.[144] However, despite extensive evaluation in clinical trials, there has been uncertainty about their role in the management of patients with acute coronary syndromes. A meta-analysis based on individual data from 35,970 patients in 11 randomized trials comparing direct thrombin inhibitors (either hirudin, bivalirudin, argatroban, inogatran, or efegatran) with heparin for management of acute coronary syndromes, demonstrated a lower risk of death or MI at the end of treatment and at 30 days with direct thrombin inhibitors than with heparin. This reduction primarily reflected a lower risk of MI. Subgroup analyses indicated a benefit of direct thrombin inhibitors in both acute coronary syndrome trials and percutaneous coronary intervention trials. A reduction in death or MI was seen with hirudin and bivalirudin, but not with univalent direct thrombin inhibitors such as argatroban, inogatran, and efegatran.[145] However, when major bleeding outcomes were analyzed by agent, hirudin was associated with an excess of major bleeding compared with heparin, while both bivalirudin and the univalent direct thrombin inhibitors had lower rates of bleeding. The characteristics of the approved direct thrombin inhibitors are highlighted in Table 22-2.

TABLE 22–2 Properties of Hirudin, Bivalirudin, and Argatroban

Property	Hirudin	Bivalirudin	Argatroban
Molecular mass	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Predominant mechanism of clearance	Renal	Proteolysis at sites other than kidneys and liver	Hepatic
Plasma half-life after intravenous administration (minutes)	40	25	45

Hirudin

Mechanism of Action

Hirudin is a 65-amino acid polypeptide originally isolated from the salivary gland of the medicinal leech. A potent and specific inhibitor of thrombin, it binds to thrombin's active site by its globular amino-terminal domain and to thrombin's substrate recognition site (exosite 1) via its carboxy-terminal domain.[146,147] Two forms of recombinant hirudin, lepirudin and desirudin, are currently available in North America and Europe. Unlike natural hirudin, recombinant hirudins lack a sulfate group on the tyrosine residue at position 63. Although this change results in a 10-fold reduction in their affinity for thrombin, recombinant hirudins still bind tightly to the enzyme, forming an almost irreversible complex.[148] The almost irreversible nature of this complex may be considered a relative weakness, because there is no available antidote should bleeding occur. Hirudin is not absorbed via the gastrointestinal tract and must be administered intravenously or by subcutaneous injection.[143] Hirudin is predominantly cleared by the kidneys and undergoes little hepatic metabolism.[143,149] It has a plasma half-life of 40 minutes after intravenous administration and approximately 120 minutes after subcutaneous injection.[143]

Indications

Lepirudin is licensed for the treatment of patients with heparin-induced thrombocytopenia, while desirudin is approved in Europe and the United States for postoperative thromboprophylaxis in patients undergoing elective hip arthroplasty. Hirudin also has been tested as an adjunct to thrombolytic therapy in patients with acute MI and as a replacement for heparin in patients with unstable angina or NSTEMI and those undergoing percutaneous coronary interventions.

Acute Myocardial Infarction with Thrombolysis. Three trials of hirudin as an adjunct to coronary thrombolysis were stopped prematurely because hirudin produced an unacceptable risk of intracranial hemorrhage.[20,21,150] Lower doses of hirudin were then assessed in three studies.[151-153] Overall, hirudin was no more effective than heparin at 30 days,[153,154] although short-term benefits at 24 hours and 48 hours were observed in one study[152] and a 35% reduction in the rate of death and reinfarction at 30 days was seen in a retrospective analysis of the subgroup of patients who received streptokinase.[153] No such favorable interaction was seen in patients receiving hirudin as an adjunct to tissue plasminogen activator (tPA).

Although critics of these studies have suggested that the hirudin dose was too low, treatment initiation too delayed, and treatment duration too short to obtain evidence of clinical efficacy, in the population of patients above, therapy with hirudin was no better than UFH in preventing adverse clinical outcomes.

Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction. Hirudin has been compared with heparin in two large trials involving patients with unstable angina or NSTEMI. Among those patients enrolled in the GUSTO-IIb trial who presented without ST-segment elevation and, therefore, did not receive thrombolytic therapy, there was no significant difference in the rate of death or MI between those who received intravenous UFH and those treated with hirudin,[155] although there was a trend for an early, but transient, benefit with hirudin. The risk of moderate bleeding was increased with hirudin. In the OASIS-2 study, hirudin was more effective than UFH during the 3 days of treatment. There was no additional gain or loss of benefit after treatment stopped and a nonstatistically significant advantage in favor of hirudin with respect to cardiovascular death or new MI was still present at days 7 and 35.[156] Combined data from the trials utilizing this agent in patients with unstable angina or NSTMI,[145,151,152,156] however, demonstrate that hirudin provides a statistically significant reduction in cardiovascular death and MI rates at both 72 hours and 7 days. Although the effect persists beyond 7 days, its impact is attenuated statistically over time.[157]

Percutaneous Coronary Interventions. Hirudin produced only transient advantages over heparin with respect to death, nonfatal MI, or need for coronary bypass surgery, stenting, or second angioplasty when used after coronary angioplasty.[145,158] Consequently, the sole use of hirudin in this setting cannot be recommended until further studies are performed.

Dosages

Hirudin's narrow therapeutic window makes monitoring of anticoagulant effect necessary, particularly when the drug is given in conjunction with thrombolytic agents.[20,21,150] Generally, treatment is monitored with the aPTT and the dose adjusted to achieve a target aPTT ratio of 1.5 to 2. The aPTT should be determined before treatment, 4 hours after the start of intravenous hirudin therapy, 4 hours after every dosage change, and then at least once daily.[159] If the aPTT is subtherapeutic, the infusion rate should be increased by 20%. If the aPTT is supratherapeutic, the aPTT should be stopped for 2 hours and if the aPTT is within the therapeutic range with re-testing, the infusion should be restarted at 50% of the previous dose.[160] Unfortunately, there are problems when the aPTT is used to monitor hirudin therapy, including variability in responsiveness between patients[161] and the lack of a linear correlation with plasma hirudin levels. Although the ecarin clotting time provides a linear correlation with hirudin levels, this test has not been standardized and is not available on a routine basis.

In patients with unstable angina or NSTEMI, hirudin has been given as a 0.4 mg/kg bolus, followed by a 0.15 mg/kg/hour infusion for 72 hours, adjusted to maintain the aPTT between 60 and 100 seconds.[156]

Side Effects

Although major bleeding has been observed to occur more frequently in patients treated with hirudin than in those receiving adjusted-dose UFH,[145,156,157] no excess of strokes or life-threatening bleeds has been demonstrated.[156,157] No specific antidote is available to neutralize hirudin. Hirudin-induced bleeding has been reversed by prothrombin complex concentrates,[162] hemodialysis, and hemofiltration.[163] Using inhibition of thrombin generation in shed blood as an index of activity, recombinant factor VIIa can reverse the

anticoagulant effect of direct thrombin inhibitors in healthy volunteers.[164] The ability of this agent to reduce bleeding induced by direct thrombin inhibitors in patients has not been established.

Antibodies against hirudin develop in up to 40% of patients treated with lepirudin. Although most of these antibodies have no clinical impact, some can prolong the plasma half-life of lepirudin, resulting in drug accumulation. In addition, anaphylaxis can occur if patients with antibodies are re-exposed to hirudin.

Contraindications and Drug Interactions

Hirudin should not be given to patients with contraindications to anticoagulants (see Box 22-1). The drug is cleared by the kidneys and dose adjustments and careful monitoring are required if this agent is used in patients with renal dysfunction.[143,159] Investigations have documented placental transfer of hirudin in rabbits and rats.[165] Although small numbers of case reports of successful outcomes with hirudin use in pregnancy have been published,[165] there are insufficient data to evaluate its safety in this setting. The risk of hemorrhage is increased when hirudin is combined with antiplatelet agents and thrombolytic drugs; the interaction when hirudin is used in combination with GP IIb/IIIa receptor antagonists, UFH, or LMWH has not been well-studied.

Bivalirudin

Mechanism of Action

Like hirudin, bivalirudin also is a bivalent inhibitor of thrombin.[166] This synthetic 20-amino acid polypeptide is comprised of an active site-directed moiety, D-Phe-Pro-Arg-Pro, linked via a tetraglycine spacer to a dodecapeptide analogue of the carboxy-terminal of hirudin[166] that interacts with exosite 1 on thrombin.[167] Unlike hirudin, bivalirudin produces only transient inhibition of the active site of thrombin because, once bound, thrombin cleaves the Arg-Pro bond within the amino-terminal of bivalirudin.[167,168] Without its amino-terminal segment, the carboxy-terminal portion of bivalirudin bound to exosite 1 is a much weaker thrombin inhibitor.[167]

Bivalirudin's plasma half-life after intravenous infusion is 25 minutes.[169] This shorter half-life may endow bivalirudin with a better safety profile than hirudin. Only a fraction of bivalirudin is renally excreted, suggesting that hepatic metabolism and proteolysis at other sites contribute to its clearance.[169] This agent must be administered parenterally.

Indications

Acute Myocardial Infarction with Thrombolysis. As a result of bivalirudin's early promise in patency trials utilizing streptokinase,[169-171] the HERO-2 trial, an open-label randomized study of 17,073 patients, was performed comparing this agent with UFH in patients receiving streptokinase for acute MI.[172] Although there was no difference between the two regimens with respect to the primary endpoint of 30-day mortality in this study, bivalirudin was associated with a reduction in the rate of reinfarction at 96 hours, a prespecified secondary endpoint. The composite net clinical benefit outcome of death, MI, and nonfatal disabling stroke favored bivalirudin. A reduction in MI in the absence of an effect on mortality is consistent with the results with other direct thrombin inhibitors.[145] Bivalirudin therapy was associated with a small but statistically significant increase in the rate of moderate bleeding. A similar trend was also seen for excess severe bleeding and intracranial hemorrhage. This was an unexpected finding given the reduced risks of bleeding seen in earlier studies performed with bivalirudin. Post-hoc subgroup analysis suggested that the excess bleeding with bivalirudin could be accounted for by the fact that, in contrast to heparin, the dose of bivalirudin was not titrated to the aPTT. Bivalirudin has not been well evaluated in patients receiving tPA or third-generation bolus thrombolytic therapy.

Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction. Early dose-ranging studies of bivalirudin in patients with unstable angina suggest that this drug is effective and well tolerated in this clinical situation.[173-175] These results, however, require confirmation in large clinical studies. Unfortunately, the TIMI 8 trial, a randomized comparison of UFH with bivalirudin in patients with unstable angina or NSTEMI, was terminated by the sponsor after only 133 of a planned 5320 patients were enrolled.[176]

Percutaneous Coronary Interventions. Bivalirudin has been studied as an alternative to heparin in patients with unstable angina undergoing percutaneous coronary angioplasty and is licensed for this indication. Initial results of the Bivalirudin (Hirulog) Angioplasty Study found bivalirudin to be no more effective than heparin for patients undergoing percutaneous coronary angioplasty, although bivalirudin produced less bleeding than high-dose heparin and was superior to heparin in the prespecified high-risk group of patients undergoing intervention for postinfarction angina.[177] However, in a reanalysis of the study results using a more contemporary definition of MI, bivalirudin was more effective than heparin at reducing the risk of death, MI, and revascularization at 6 months.[178] Moreover, there was a marked relative risk reduction in bleeding complications in bivalirudin-treated patients compared with those receiving UFH. Based on this reanalysis and recent meta-analyses,[145,179] bivalirudin appears to be an effective alternative to heparin in patients undergoing coronary angioplasty.

Bivalirudin was compared with the combination of UFH and GP IIb/IIIa inhibitor in the REPLACE-2 study, a phase III trial of 6010 patients undergoing percutaneous intervention. Participants were randomized to bivalirudin plus a provisional GP IIb/IIIa inhibitor (abciximab or eptifibatide) or UFH plus GP IIb/IIIa inhibitor.[180] Bivalirudin was given as a 0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/hour during the procedure. Use of a GP IIb/IIIa antagonist was required in only 7% of patients randomized to bivalirudin. The use of bivalirudin resulted in a nonstatistically significant reduction in the primary outcome, a composite of death, MI, urgent revascularization, or major bleeding at 30 days. However, rates of major bleeding were significantly lower in patients given bivalirudin than in those treated with UFH.

The ACUITY study compared three antithrombotic strategies in patients presenting with NSTEMI scheduled to be treated with an early invasive strategy. The investigators randomized 13,819 patients to receive one of either bivalirudin plus provisional GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, or intravenous UFH/enoxaparin plus GP IIb/IIIa inhibitor.[181] Clopidogrel was added to aspirin at the discretion of the local investigator and 57% of patients underwent percutaneous coronary intervention during study drug administration. In this trial, bivalirudin was started before angiography and was given as a bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/hour. A second bolus of 0.5 mg/kg was given immediately prior to percutaneous coronary intervention followed by an infusion of 1.75 mg/kg/hour during the procedure. Bivalirudin plus provisional GP IIb/IIIa inhibitor, as well as bivalirudin plus GP IIb/IIIa inhibitor, were noninferior to intravenous UFH/enoxaparin for the composite of death, MI, or unplanned revascularization at 30 days provided that clopidogrel was given before or at least 30 minutes after the procedure. While bivalirudin plus GP IIb/IIIa inhibitor therapy was noninferior to UFH plus GPIIb/

IIa inhibitor for clinically important bleeding, bivalirudin plus provisional GP IIb/IIIa inhibitor was superior to the UFH arm for this endpoint.

Bivalirudin also has been evaluated in patients with STEMI. In the HORIZONS AMI trial,[182] 3600 patients were randomized within 12 hours of symptom onset to either bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/hour) plus provisional GP IIb/IIIa antagonist or to UFH (60 units/kg with subsequent doses titrated to achieve a target ACT of 200 to 250 seconds) along with a GP IIb/IIIa antagonist. All patients underwent percutaneous coronary intervention. Of those randomized to bivalirudin, 7.2% received a GP IIb/IIIa antagonist. Compared with heparin plus a GP IIb/IIIa antagonist, bivalirudin did not reduce the primary endpoint of all-cause mortality, reinfarction, target vessel revascularization (TVR) or stroke, but did reduce major bleeding by 40% (from 8.3% to 4.9%; $P < .0001$). Bivalirudin also reduced the risk of cardiovascular mortality compared with heparin plus a GP IIb/IIIa antagonist (1.8% and 2.9%, respectively; $P = .035$).

Thus, it appears that bivalirudin is an effective anticoagulant in patients with acute coronary syndromes, particularly for those undergoing percutaneous coronary intervention. Bivalirudin may obviate the need for a GP IIb/IIIa inhibitor and, therefore, reduce bleeding risks. GP IIb/IIIa inhibitors may still be required in very high risk patients.

Dosages

In contrast to hirudin, there is no evidence that bivalirudin requires coagulation monitoring in patients undergoing coronary angioplasty, because the drug is safe when given in weight-adjusted doses (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/hour during the procedure).[180-182] In contrast, the results of the HERO-2 trial suggest that the dose of bivalirudin should be titrated to achieve an aPTT 1.5 to 2.5 times control if bivalirudin is used as an adjunct to streptokinase and aspirin for treatment of acute MI.[169]

Side Effects

It has been suggested that the principal benefit of bivalirudin appears to be a reduction in the risk of major hemorrhage. In contrast to hirudin, bivalirudin is not immunogenic. However, antibodies against hirudin can cross-react with bivalirudin in vitro. The clinical significance of this cross-reactivity is unknown.

Contraindications and Drug Interactions

Bivalirudin is contraindicated in patients with the conditions listed in Box 22-1. The concomitant use of antiplatelet agents, other anticoagulants, or thrombolytic agents with bivalirudin increases the risk of hemorrhage.

ACTIVE SITE–DIRECTED DIRECT THROMBIN INHIBITORS

Argatroban

A carboxylic acid derivative that is metabolized in the liver, argatroban binds noncovalently to the active site of thrombin.[183] This agent has a half-life of 20 to 60 minutes and prolongs the aPTT in a dose-dependent manner. Argatroban is extensively metabolized in the liver and its plasma levels are not influenced by renal function.[183] This drug is an effective alternative to heparin in patients with HIT and is approved for this indication. In preliminary evaluation in patients with acute STEMI receiving thrombolysis, argatroban has been associated with similar bleeding risks as UFH.[184,185] Definitive clinical trials in patients with acute coronary syndromes have not been performed.

Ximelagatran

Ximelagatran, an uncharged lipophilic drug with little intrinsic activity against thrombin, is a prodrug of melagatran, an active site–directed thrombin inhibitor. Ximelagatran is well absorbed from the gastrointestinal tract and undergoes rapid biotransformation to melagatran.[186,187] The drug produces a predictable anticoagulant response after oral administration and little or no coagulation monitoring appears to be necessary. Ximelagatran was evaluated for prevention and treatment of venous thromboembolism, prevention of cardioembolic events in patients with nonvalvular atrial fibrillation, and prevention of recurrent ischemia in patients with recent MI.[188] Although initial studies led to the temporary approval of ximelagatran in Europe for thromboprophylaxis in patients undergoing major orthopedic surgery, the drug was eventually withdrawn from the world market because of an increased risk of hepatic toxicity.[188,189] Despite this disappointing outcome, the studies involving ximelagatran showed that effective oral anticoagulation does not necessarily require monitoring.

Dabigatran Etexilate

Dabigatran etexilate is a double prodrug that is absorbed from the gastrointestinal tract with a bioavailability of approximately 6%.[190] Once absorbed, dabigatran etexilate is converted by esterases into its active metabolite, dabigatran (BIBR 953). Dabigatran is a reversible inhibitor that targets the active site of thrombin. Cytochrome P-450 (CYP450) plays no relevant role in this drug's metabolism; therefore, the potential for clinically relevant interactions between dabigatran and drugs metabolized by CYP450 is low.[191] Plasma levels of dabigatran peak at 1.5 hours and dabigatran has a half-life of 8 hours after a single dose and up to 17 hours after multiple doses.[190] Thus, it may be possible to administer dabigatran etexilate once daily for some indications. Dabigatran is excreted unchanged via the kidneys; therefore, this drug is contraindicated in patients with renal failure.[190]

Dabigatran has shown promise in phase II and III studies of thromboprophylaxis in patients undergoing hip or knee arthroplasty[191-194] and dabigatran etexilate has been approved for this indication in Europe and Canada. The ability of dabigatran etexilate to prevent atrial fibrillation-related stroke was evaluated in the phase II PETRO study and PETRO-EX, its open-label extension.[195,196] In the PETRO study, 502 patients with atrial fibrillation were randomized to one of three doses of dabigatran etexilate alone or combined with aspirin (81 to 325 mg per day) or to warfarin for 12 weeks. Dabigatran etexilate dosed at 150 mg twice daily compared favorably to warfarin, whereas the lowest dose of 50 mg twice daily was ineffective and the highest dose of 300 mg twice daily was associated with an increased risk of major bleeding.[195] In the phase III RELY study, 18,113 patients with atrial fibrillation were randomized to one of two blinded doses of dabigatran etexilate (150 mg twice daily or 110 mg twice daily) or to open-label dose-adjusted warfarin (INR target 2.0 to 3.0). Annual rates of the primary efficacy outcome, stroke or systemic embolism, were 1.69% in the warfarin group, 1.53% in those receiving 110 mg of dabigatran ($P < 0.001$ for noninferiority) and 1.11% in the group given 150 mg of dabigatran ($P < 0.001$ for both noninferiority and superiority). Annual rates of major bleeding were 3.36% in the warfarin group, 2.71% in the group receiving 110 mg of dabigatran ($P = 0.003$) and 3.11% in those given 150 mg of dabigatran ($P = 0.31$). Rates of hemorrhagic stroke were lower with both doses of dabigatran than with warfarin.[196] There was no signal for elevated levels of liver transaminases in patients receiving dabigatran etexilate.[191-193,195] Dabigatran also underwent phase II evaluation for prevention of recurrent ischemic events in patients with acute coronary syndromes.

INHIBITORS OF INITIATION OF COAGULATION

Since TF in disrupted atherosclerotic plaques initiates thrombosis, alternative therapeutic approaches have focused on the development of agents that target the factor VIIa/TF complex and block the initiation of coagulation.[4] The drugs in the most advanced stage of development are recombinant TF pathway inhibitor (TFPI) or tifacogin and nematode anticoagulant peptide (NAPc2). Active site–blocked factor VIIa (factor VIIai) also has been evaluated in humans.

Tifacogin

Tissue factor pathway inhibitor (TFPI) or tifacogin forms a complex with factor Xa that binds to factor VIIa/TF and inhibits thrombin generation.[197] Only small amounts of TFPI circulate in the blood in the free state. Most of the circulating TFPI is associated with lipoproteins or is bound to the endothelium. Additional TFPI is stored in platelets.[198] Full-length TFPI is released from the endothelium when heparin or LMWH is given, presumably because these agents displace TFPI bound to endothelial glycosaminoglycans. When administered intravenously, TFPI has a short half-life because it is rapidly cleaved into nonfunctional truncated forms by an unknown protease. In pigs, TFPI attenuates injury-induced neointimal hyperplasia and it inhibits smooth muscle cell migration in vitro.[199] TFPI attenuates the coagulopathy and improves survival in sepsis models in animal models.[200-202]

Tifacogin, a recombinant form of TFPI, has been evaluated in patients with sepsis. Based on promising phase II results,[203] a large phase III clinical trial comparing this agent with placebo in patients with severe sepsis was initiated.[204] The primary endpoint of 28 day mortality was similar in patients randomized to tifacogin compared with those allocated to placebo, while the rate of bleeding was higher in tifacogin-treated patients. A recently completed phase III clinical trial compared two doses of tifacogin with placebo in patients with severe community acquired pneumonia. The drug has not been evaluated for prevention or treatment of thrombosis.

Nematode Anticoagulant Protein c2 (NAPc2)

NAPc2, an anticoagulant protein isolated from the nematode *Ancylostoma caninum*, binds to a noncatalytic site on both factor X and factor Xa and inhibits factor VIIa within the factor VIIa/TF complex.[205] Therefore, functionally, NAPc2 behaves much like TFPI. Because NAPc2 binds to factor X, as well as factor Xa, it has a half-life of almost 50 hours after subcutaneous injection. In a phase II study, NAPc2 showed promise in preventing venous thromboembolism after elective knee replacement surgery.[206] Current studies with this agent are focusing on arterial thrombosis. In the dose-ranging ANTHEM-TIMI 32 trial, 203 patients with unstable angina or NSTEMI were randomized to intravenous rNAPc2 in doses ranging from 1.5 to 10 μg/kg or placebo every 48 hours for up to three doses.[207] All patients received aspirin, UFH or enoxaparin, and early catheterization. Clopidogrel and GP IIb/IIIa blockers were encouraged. Doses of rNAPc2 of 7.5 μg/kg or greater suppressed prothrombin fragment 1.2 levels and reduced ischemia, as detected by continuous electrocardiography. Although rNAPc2 was well tolerated, all the observed major hemorrhages occurred in the highest dose of 10 μg/kg. In a second multicenter, placebo-controlled, randomized, dose-escalating trial, adjunctive NAPc2 (in doses ranging from 3.5 to 10 μg/kg) suppressed levels of prothrombin fragment 1.2 in patients undergoing percutaneous coronary intervention.[208] Bleeding rates for doses ranging from 3.5 to 7.5 μg/kg were comparable to that seen with placebo, whereas an increased rate was observed in the 10 μg/kg group.

Active Site–Blocked Factor VIIa (FVIIai)

Active site–blocked factor VIIA (FVIIai), a form of recombinant FVIIa that has its active site irreversibly blocked, is a competitive inhibitor of TF-dependent factor IX or X activation. In both in vitro studies and animal studies, infusions of FVIIai prevented thrombus formation on artificial surfaces or injured vasculature.[209-214] Based on these promising results, FVIIai in doses ranging from 50 to 400 μg/kg with or without adjunctive heparin was compared with heparin alone in 491 patients undergoing elective percutaneous coronary intervention.[215] FVIIai alone or with heparin produced no significant reduction in the primary endpoint, a composite of death, MI, need for urgent revascularization, abrupt vessel closure, or bailout use of GP IIb/IIIa antagonists at day 7 or hospital discharge. Rates of major bleeding were similar with FVIIai and heparin. Consequently, this agent has not been developed further for treatment of arterial thrombosis.

INHIBITORS OF PROPAGATION OF COAGULATION

The propagation of coagulation can be inhibited by drugs that target factors IXa or Xa or by agents that inactivate their respective cofactors, factor VIIIa or factor Va.

Factor IXa Inhibitors

Factor IXa is essential for amplification of coagulation.[216] Both parenteral and oral factor IXa inhibitors are under development. RB006 is a parenterally administered RNA aptamer that binds factor IXa with high affinity.[217] In a phase I study, RB006 produced rapid anticoagulation, as evidenced by a dose-dependent prolongation of the aPTT.[218] The potential use of a complementary oligonucleotide (RB007) for rapid neutralization is being explored in the cardiopulmonary bypass surgery setting.[219]

TP889 is an orally active direct factor IX inhibitor that has demonstrated antithrombotic potential in animal models of venous and arterial thrombosis.[220] However, in a phase II randomized study comparing 9 days of TTP889 (300 mg once daily) with placebo for prevention of venous thromboembolism in patients who had received 6 to 10 days of standard prophylaxis after hip fracture surgery, there was no reduction in the primary efficacy outcome (deep vein thrombosis on mandatory venography at study completion or symptomatic venous thromboembolism during treatment) with the use of active therapy.[221] There were no major bleeding events and only two clinically relevant non-major bleeding events with TTP889. Although this suggests that the dose evaluated may not have been appropriate, there was no evidence to suggest that patients with the highest plasma TTP889 concentrations had lower rates of venous thromboembolism than those with lower drug levels. Consequently, development of TTP 889 was halted.

New Factor Xa Inhibitors

Drugs that inhibit factor Xa interfere with the conversion of prothrombin to thrombin and attenuate the fibrin formation.[5] Both direct and indirect factor Xa inhibitors are under investigation. Direct factor Xa inhibitors bind directly to the active site of factor Xa and block its interaction with its substrates. These drugs include recombinant analogues of natural factor Xa inhibitors, as well as synthetic small molecules of Xa. The ability of the direct factor Xa inhibitors to access and inhibit platelet-bound factor Xa,[222] in addition to free factor Xa, may endow them with a potential advantage of these agents over the indirect factor inhibitors, such as fondaparinux.

Newer indirect factor Xa inhibitors include novel pentasaccharide derivatives, including idraparinux, SSR12517E, and SR123781A.

Natural Inhibitors

The natural inhibitors of factor Xa tick anticoagulant peptide (TAP)[223] and antistasin[224] were originally isolated from the soft tick and the Mexican leech, respectively. Both are available in recombinant forms. TAP is a 60-amino-acid polypeptide that forms a stoichiometric complex with factor Xa.[223] TAP appears to bind to factor Xa in a two-step fashion[223] in which an initial low affinity interaction involving a site distinct from the catalytic site of the enzyme is followed by a high affinity interaction with the active site, resulting in the formation of a stable enzyme inhibitor complex. Antistasin, a 119-amino-acid polypeptide, is also a tight-binding, slowly reversible inhibitor of factor Xa.[225] TAP and antistasin have been shown to reduce arterial thrombosis[226,227] and restenosis[228] in animal models. Because they are antigenic, neither agent has been tested in humans.

Synthetic Inhibitors

The synthetic direct factor Xa inhibitors include parenteral agents, such as DX-9065a and otamixaban, and a number of orally active agents. The latter include apixaban, rivaroxaban, LY-517717, and YM-150.

DX-9065a

DX-9065a[229] is a synthetic nonpeptidic, low-molecular-weight, reversible inhibitor of factor Xa that is cleared by the kidneys. Although DX-9065a exhibits oral bioavailability,[230] high doses must be given to produce an antithrombotic effect and, therefore, the drug is administered parenterally.

DX-9065a has been evaluated in patients with non-ST-elevation acute coronary syndromes and in patients undergoing percutaneous interventions. In the acute coronary syndrome trial, 402 patients were randomized to weight-adjusted heparin or to one of two doses of DX-9065a.[231] All patients received aspirin and an early invasive management approach was recommended. There was no difference in the primary efficacy endpoint (a composite of death, MI, urgent revascularization or ischemia) between the three treatment arms. However, major bleeding occurred in less than 1% of patients who received DX-9065a, compared with 3.3% of those treated with heparin. In the study involving patients undergoing percutaneous coronary interventions, 175 patients were randomized to open-label DX-9065a or to heparin in one of four sequential phases.[232] Although thrombotic events were rare in all phases of the study, enrollment was stopped early in the phase evaluating the lowest dose of DX-9065a because of catheter thrombosis. Major bleeding events were uncommon and there was no apparent dose response. Although promising, DX-9065a has not undergone further clinical evaluation.

Otamixaban

Otamixaban is a noncompetitive inhibitor of factor Xa that is administered intravenously and has a half-life of 2 to 3 hours.[233] In a phase IIa study comparing a 24-hour infusion of this medication with placebo in patients with stable coronary artery disease, the addition of otamixaban to usual medications did not cause bleeding and otamixaban produced a rapid and sustained increase in anti-factor Xa activity.[234] In a subsequent double-blind, parallel-group, dose ranging study of patients undergoing nonurgent percutaneous coronary intervention, an intravenous otamixaban bolus of 0.140 mg/kg followed by an infusion of 0.2mg/kg lowered prothrombin fragment 1+2 levels more than UFH and was not associated with an increased risk of bleeding.[235] A phase II trial comparing otamixaban with UFH in patients with moderate-to-high risk non–ST-segment elevation acute coronary syndrome and planned early invasive strategy showed favorable efficacy and safety for intermediate otamixaban doses.[235a]

Apixaban

Apixaban is a high affinity, highly selective reversible factor Xa inhibitor with high oral bioavailability and a half-life of approximately 12 hours.[236] Food has no effect on apixaban's absorption and the drug produces a predictable anticoagulant effect. Apixaban is cleared through both the fecal and renal route with the latter accounting for about 25% of drug clearance.[236]

Based on the results of a phase II trial that evaluated six doses of apixaban compared with enoxaparin or warfarin in patients undergoing knee replacement surgery,[237] a dose of 2.5 mg apixaban twice daily has been compared with enoxaparin in two phase III trials in patients undergoing knee replacement surgery and in one trial of patients undergoing hip replacement surgery.[238] The same dose is undergoing evaluation for thromboprophylaxis in medical patients. A phase II dose-finding trial of apixaban for treatment of deep vein thrombosis has been completed,[239] with a dose of 20 mg daily resulting in a lower frequency of the primary composite outcome of symptomatic venous thromboembolism and worsening thrombotic burden (as assessed by follow-up leg ultrasounds and lung scans) than conventional therapy. There was no clinically relevant or statistically significant difference in the frequency of major bleeding in apixaban arms compared with the standard therapy group. There was no evidence of hepatotoxicity in the apixaban-treated patients. Apixaban is being evaluated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in two phase III trials. In the ARISTOTLE trial, apixaban is being compared with warfarin dose-adjusted to achieve a target INR of 2.0 to 3.0; while in the AVERRROES trial, patients with atrial fibrillation and at least one risk factor for stroke who are considered unsuitable for vitamin K antagonist therapy are randomized to apixaban or aspirin. A phase II trial of apixaban for thromboprophylaxis in patients with cancer has been completed. A phase III trial examining the utility of apixaban for secondary prevention in acute coronary syndrome patients is ongoing.

Rivaroxaban

Rivaroxaban is another highly selective factor Xa inhibitor that has an oral bioavailability of 80% and a half-life of approximately 9 hours.[240] The clearance of rivaroxaban is predominantly renal with 75% of the drug cleared via the kidneys.[240]

This drug has been evaluated for thromboprophylaxis in patients undergoing knee or hip arthroplasty in four phase II trials.[241-245] Based on the results of these studies, phase III studies in major orthopedic studies used a 10-mg once-daily dose. In the RECORD 1 study,[246] rivaroxaban and enoxaparin were both administered for 5 weeks following total hip replacement; while in the RECORD 2 study,[247] patients undergoing total hip arthroplasty were randomized to either rivaroxaban for 35 ± 1 days or enoxaparin for 10 to 14 days, followed by placebo. The RECORD 3 study[248] enrolled patients undergoing total knee arthroplasty. In this study, both enoxaparin and rivaroxaban were continued for 10 to 14 days. In all three studies, the frequency of the primary efficacy endpoint of deep vein thrombosis as detected on mandatory venography, nonfatal symptomatic venous thromboembolism, and all-cause mortality was less frequent in those treated with rivaroxaban than in those randomized to enoxaparin. There was no significant difference in bleeding complications between the two study drugs. Based on the results

of these trials, rivaroxaban has been licensed for thromboprophylaxis after hip or knee replacement surgery in Europe and Canada.

Rivaroxaban has also been evaluated for treatment of proximal deep vein thrombosis in two dose-ranging studies.[249,250] Based on the results of these studies, ongoing phase III venous thromboembolism treatment studies are comparing 3 weeks of rivaroxaban 15 mg twice daily, followed by 20 mg once daily with standard therapy. In studies of stroke prevention in patients with atrial fibrillation at high risk of stroke, a rivaroxaban dose of 20 mg once daily is being used.

Rivaroxaban has been shown to be effective in the prevention of arterial thrombosis occlusion in the rat carotid artery injury model.[251] A phase III study evaluating the safety and efficacy of rivaroxaban in combination with aspirin alone or with aspirin and a thienopyridine in patients with acute coronary syndromes is currently recruiting patients.

LY-517717

LY-517717, a direct factor Xa inhibitor, is orally available and has a half-life of about 25 hours. It is given once daily. LY-517717 was evaluated in a phase II noninferiority study that randomized 511 patients undergoing hip or knee arthroplasty to one of six doses of LY-517717 or once-daily subcutaneous enoxaparin.[252] Both treatments were administered for six to 10 doses. Randomization to the three lower doses of the experimental agent was stopped early due to lack of efficacy, while the three higher doses had efficacy similar to that of enoxaparin. Adjudicated major bleeding events were uncommon in all study arms. Additional studies are needed to determine the efficacy, safety, and optimal dose of this agent.

YM-150

YM-150, a orally active anti-factor Xa inhibitor, is also given once daily. In a dose-escalation study of 174 patients undergoing elective hip arthroplasty, no major bleeds were reported and there was no dose-response trend for clinically relevant nonmajor bleeding.[253] However, there was a statistically significant dose response for efficacy (venous thromboembolism detected on bilateral venography at the end of 7 to 10 days of treatment or objectively confirmed symptomatic deep vein thrombosis or pulmonary embolism). Although the point estimates for deep vein thrombosis appeared to favor the two highest doses of YM-150 over enoxaparin, the small study sample size precludes any firm conclusions. A second phase II trial in patients undergoing elective hip arthroplasty is planned, while phase II studies in patients undergoing total knee replacement are ongoing. A safety and tolerability study in patients with atrial fibrillation has been completed.

Edoxaban (DU-176b)

Edoxaban is another orally active, small molecular direct factor Xa inhibitor that has been evaluated in an open-label phase IIa dose-finding study for the prevention of venous thromboembolism after total hip replacement. The results of this study have yet to be published. Building on phase II data in atrial fibrillation, a large phase III trial is comparing two different doses of edoxaban (30 or 60 mg once daily) with warfarin for stroke prevention.

Betrixaban (PRT-054021)

In a 200-patient phase II study comparing two doses of PRT-054021 (15 mg twice daily or 40 mg twice daily) with enoxaparin 30 mg twice daily for 10 to 15 days following unilateral knee replacement, this orally active agent appeared both safe and effective.[254] Additional trials in the prevention and treatment of venous thromboembolism, as well as in patients with atrial fibrillation are planned.

Idraparinux

A hypermethylated derivative of fondaparinux, idraparinux binds antithrombin with such affinity that its plasma half-life of 80 hours is similar to that of antithrombin.[255] Because of its long half-life, idraparinux can be given subcutaneously once per week. Based on the promising results of a phase II dose-finding trial in which idraparinux was compared with warfarin in patients with proximal deep vein thrombosis,[256] two randomized noninferiority phase III trials were conducted in patients with deep vein thrombosis or pulmonary embolism.[257] In these studies, patients received either 2.5 mg of idraparinux subcutaneously once per week or conventional therapy (low-molecular-weight heparin or UFH followed by an adjusted-dose vitamin K antagonist) for 3 or 6 months. Although the frequency of recurrent venous thromboembolism was similar in the idraparinux and conventionally treated groups in the deep vein thrombosis trial, in the pulmonary embolism patients, idraparinux was less effective than conventional therapy. This difference in efficacy was due to an excess of early fatal and nonfatal recurrences of pulmonary embolism and was associated with an increase in total mortality. In both studies, bleeding rates in the idraparinux-treated patients were similar to or lower than those in the conventional-therapy groups.

The efficacy of long-term idraparinux was evaluated in an extension study in which patients who had completed 6 months of initial treatment of deep vein thrombosis or pulmonary embolism with either idraparinux or a vitamin K antagonist were randomized to an additional 6 months of treatment with either once-weekly subcutaneous idraparinux or placebo.[258] Although idraparinux therapy was effective in preventing recurrent venous thromboembolism, its use was associated with an increased risk of major hemorrhage (including three fatal intracranial bleeds). Thus, the net clinical benefit of extended treatment with idraparinux appears marginal, at best.

The AMADEUS trial[259] compared once-weekly idraparinux with a vitamin K antagonist in patients with atrial fibrillation. After 4576 patients were enrolled, the trial was stopped prematurely because of excess bleeding in those randomized to idraparinux. Intracranial bleeding also was more frequent with idraparinux. Elderly patients and those with renal insufficiency appeared to have the highest risk of bleeding with idraparinux suggesting that a reduced dose is needed in such patients. Given these results, it is unlikely that idraparinux will be developed further. Instead, attention has shifted to idrabiotaparinux.

Idrabiotaparinux (SSR12517E)

A biotinylated form of idraparinux, idrabiotaparinux exhibits the same pharmacokinetic and pharmacodynamic profile as idraparinux. Like idraparinux, idrabiotaparinux is given subcutaneously on a once-weekly basis. The only difference is that the anticoagulant activity of idrabiotaparinux can be rapidly neutralized by intravenous administration of avidin, a large tetrameric protein derived from egg white, that binds to idrabiotaparinux to form a 1 : 1 stoichiometric complex that is cleared via the kidneys. Idrabiotaparinux is now undergoing phase III evaluation in patients with pulmonary embolism and in those with atrial fibrillation.

SR123781A

A hexadecasaccharide, SR123781A, is composed of the antithrombin-binding synthetic pentasaccharide plus a thrombin-binding sulfated tetrasaccharide joined together by a central nonsulfated heptasaccharide.[260] SR123781A binds antithrombin with high affinity.[259] In addition to catalyzing factor Xa inhibition by antithrombin, SR123781A is long enough to bridge antithrombin to thrombin and so is able to enhance

thrombin inhibition. Thus, SR12378A catalyzes inhibition of factor Xa and thrombin just like heparin. However, unlike heparin, SR123781A does not bind platelet factor 4; therefore, heparin-induced thrombocytopenia is unlikely to occur with SR123781A. In contrast to heparin, SR123781A does not bind fibrin. Because it does not form a ternary complex with fibrin and thrombin that protects thrombin from inhibition,[261] SR123781A appears capable of inhibiting fibrin-bound thrombin.[262] SR123781A exhibits almost complete bioavailability after subcutaneous administration and produces a dose-proportional increase in the aPTT and anti-factor Xa activity. The drug is primarily cleared by the kidney where it is excreted intact. A phase II study evaluating SR173781A for prophylaxis in patients undergoing elective hip arthroplasty has been completed. Although the results have yet to be reported, SR123781A does not appear to be undergoing further development.

INHIBITORS OF FACTORS VIIIa AND Va

Factors VIIIa and Va, key cofactors for intrinsic tenase and prothrombinase, respectively, are critical for propagation of coagulation. Both cofactors are inactivated by activated protein C, a naturally occurring anticoagulant that is generated when thrombin binds to thrombomodulin, producing a complex that activates protein C. Strategies aimed at enhancing the protein C anticoagulant pathway include administration of protein C or activated protein C concentrates or soluble thrombomodulin.

Drotrecogin Alpha (Activated)

Both plasma-derived and recombinant forms of protein C and activated protein C are available. In a phase III trial, intravenous recombinant activated protein C, known as drotrecogin alpha (activated), reduced mortality in patients with severe sepsis when compared with placebo, albeit with a nonstatistically significant increase in the risk of major bleeding.[263] These findings prompted licensing of recombinant activated protein C for adults with severe sepsis at high risk of death (as determined by an Acute Physiology and Chronic Health Evaluation [APACHE] II score of 25 or greater) or with failure of at least two organ systems. Since approval, two additional clinical trials, one in adults with sepsis and a low risk of death[264] and the other in children with sepsis,[265] were stopped prematurely due to lack of efficacy and the potential to cause harm because of bleeding. Based on these studies, drotrecogin alpha (activated) appears to have a limited role in patients with sepsis.

ART-123

Like membrane-bound thrombomodulin, soluble thrombomodulin complexes thrombin and induces a conformational change in the active site of the enzyme that abolishes its procoagulant activity and converts it into a potent activator of protein C. Recombinant soluble thrombomodulin, ART-123, has nearly 100% bioavailability after subcutaneous injection and a half-life of 2 to 3 days after subcutaneous injection.[266] It has been shown to be an effective antithrombotic agent in a variety of animal models.[267,268] A phase II trial examining the utility of soluble thrombomodulin for thromboprophylaxis after elective hip arthroplasty demonstrated a dose response both for efficacy (a composite of venographically detected deep vein thrombosis and symptomatic venous thromboembolism) and safety (major bleeding).[269] ART-123 has shown promise in the management of disseminated intravascular coagulation (DIC)[270] and is currently being evaluated in a placebo-controlled randomized study in patients with sepsis and DIC.

VITAMIN K ANTAGONISTS

Mechanism of Action

Coumarin derivatives are vitamin K antagonists that interfere with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide).[271] Vitamin K acts as a cofactor for post-translational carboxylation of glutamic acid residues found on the amino-terminal of vitamin K-dependent coagulation factors (factors II, VII, IX, and X) and anticoagulant proteins (protein C and protein S).[271] Gamma-carboxylation is a prerequisite for calcium-dependent interaction of these coagulation proteins with activated phospholipid surfaces. Carboxylation of vitamin K-dependent cofactors is catalyzed by a carboxylase that requires the reduced form of vitamin K. During this reaction, reduced vitamin K is oxidized to vitamin K epoxide, which is recycled back to vitamin K by vitamin K epoxide reductase. Vitamin K is then converted to reduced vitamin K by vitamin K reductase. The vitamin K antagonists inhibit vitamin K epoxide reductase and, to a lesser extent, vitamin K reductase (Fig. 22-5). With depletion of reduced vitamin K, carboxylation of the vitamin K-dependent proteins is inhibited. The antithrombotic effect of coumarin derivatives, which probably reflects lowered factor II (prothrombin) and factor X levels, is delayed for 72 to 96 hours.

Indications

Although oral anticoagulants have been used in patients with ischemic heart disease for close to half a century, their role in this patient population remains controversial.

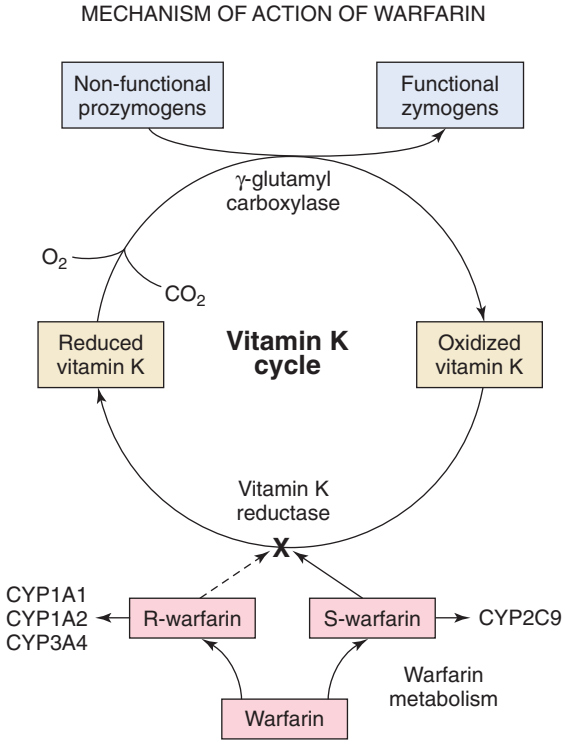

FIGURE 22–5 Mechanism of action of warfarin: A racemic mixture of S- and R-enantiomers, it is S-warfarin that is most active. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K-dependent γ-carboxylation of factors II, VII, IX and X because reduced vitamin K serves as a cofactor for a γ-glutamyl carboxylase that catalyzes the γ-carboxylation process, thereby converting prozymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces. S-warfarin is metabolized by CYP2C9. Common genetic polymorphisms in this enzyme can influence warfarin metabolism. Polymorphisms in the C1 subunit of vitamin K reductase (VKORC1) also can affect the susceptibility of the enzyme to warfarin-induced inhibition, thereby influencing warfarin dosage requirements.

Acute Myocardial Infarction. High-intensity oral anticoagulant treatment (target INR 2.8-4.8) after MI produces a reduction in mortality and clinically important vascular outcomes but is associated with a significant risk of major bleeding, including hemorrhagic stroke.[272-278] Moderate-intensity oral anticoagulation (INR 2.0-3.0) is more effective than placebo[279,280] and aspirin[277,281] at reducing recurrent ischemic events.

The addition of low, fixed-dose warfarin (1 or 3 mg)[282] or low-intensity warfarin (target INR less than 2.0)[283] to aspirin in patients with a recent MI does not appear to provide clinical benefit beyond that achieved with aspirin alone. Although the combination of aspirin with long-term moderate-intensity warfarin appears to result in lower rates of death, new MI, and stroke than aspirin alone, this benefit occurs at the expense of an appreciable increase in bleeding and therapeutic complexity.[156,277,278,281,283,284]

While both aspirin and oral anticoagulants are more effective than placebo after MI, the increased rate of major hemorrhage and the greater cost and complexity of oral anticoagulant therapy make aspirin a better choice in most patients. Oral anticoagulation is an alternative for patients at increased risk of thromboembolism (i.e., during the first 3 months after anterior MI, patients with MI complicated by severe left ventricular dysfunction, as well as those with congestive heart failure, previous emboli, evidence of mural thrombi, or atrial fibrillation) and for those who cannot tolerate aspirin.[277,278]

Primary Prevention of Ischemic Heart Disease. Low-intensity warfarin (target INR of 1.5) confers protection against fatal and nonfatal manifestations of ischemic heart disease in high-risk men, as does the combination of low-intensity warfarin and 75 mg of aspirin daily.[285] Combined treatment appears to be more effective than either warfarin or aspirin alone. However, the adverse effects associated with warfarin therapy are greater than those of aspirin and monitoring of warfarin treatment is laborious. Consequently, low-intensity warfarin, with or without aspirin, cannot be recommended for the primary prevention of MI. In individuals who cannot tolerate aspirin, however, warfarin may be a useful alternative, and combination therapy can be considered in patients at high risk for ischemic events.

Peripheral Arterial Disease. Patients with peripheral arterial disease are at risk of MI, stroke, and cardiovascular death. Antiplatelet agents, such as aspirin or clopidogrel, reduce this risk. The WAVE trial examined whether adding warfarin to antiplatelet therapy provided additional benefit.[286] A total of 2161 patients were randomized to antiplatelet therapy alone or to antiplatelet therapy plus warfarin (dose adjusted to achieve an INR of 2 to 3). Myocardial infarction, stroke, or cardiovascular death occurred in 12.2% of patients receiving combination therapy and in 13.3% of those given antiplatelet therapy alone (relative risk [RR], 0.92; 95% CI 0.73-1.16; $P = .48$). However, life-threatening bleeding was more frequent with combination therapy than with antiplatelet therapy (4.0% and 1.2%, respectively; RR 3.41; 95% confidence interval (CI) 1.84-6.35; $P < .001$). Based on these results, adding warfarin to antiplatelet therapy does not appear to improve efficacy and is associated with an increase in life-threatening bleeding.

Dosages

The prothrombin time (PT) is sensitive to reductions in three of the four vitamin-K-dependent clotting factors, prothrombin, factor VII, and factor IX. Because commercially available thromboplastin reagents vary in their sensitivity to reductions in these three clotting factors, the adequacy of warfarin dosing is measured using a standardized method of PT reporting. The international normalized ratio (INR) is based on the use of an international sensitivity index (ISI) assigned to each thromboplastin reagent that standardizes sensitivity to reductions in vitamin K-dependent clotting factors against an international reference preparation provided by the World Health Organization. The PT is converted to an INR by using the formula INR = (observed PT/mean normal PT)^{ISI}.[271]

Vitamin K antagonists have a narrow therapeutic window, and a highly variable dose-response relation.[271] Consequently, the use of these agents can be complicated by serious bleeding and their anticoagulant effect must be monitored closely by laboratory tests. The total dose of warfarin required to reach a therapeutic INR varies from patient to patient. This inter-individual variation in warfarin dosing may reflect differences in age, weight, liver function, diet, alcohol intake, concomitant medications, and comorbid illnesses.[271] Single nucleotide polymorphisms (SNPs) in the cytochrome P450 CYP2C9 system and in the gene that encodes vitamin K epoxide reductase complex 1 (VKORC1), the enzyme target of warfarin (see Fig. 22-5), influence the warfarin dose required to achieve, as well as maintain, a therapeutic INR.[287] However, the benefit that testing for these genotypes adds to conscientious INR monitoring and dose adjustment remains to be determined.

High-intensity and moderate-intensity warfarin therapy, as well as moderate-intensity warfarin combined with aspirin, have been shown to reduce adverse vascular outcome after MI. However, bleeding complications increase as INR intensity increases.[271] Fixed low-dose warfarin and low-intensity warfarin regimens (INR <2.0) have not been shown to be effective in this patient population. The decision to use warfarin alone or in combination with aspirin should be based on a careful review of the risks of future vascular and bleeding events, patient compliance with therapy, and the availability of high quality warfarin monitoring. Although aspirin is likely to remain first-line therapy for most patients with coronary artery disease, warfarin therapy may be useful in higher risk patients and those who suffer recurrent events despite aspirin treatment.

Side Effects

Bleeding is the most frequent complication of warfarin therapy. The risk of bleeding is influenced by the intensity of anticoagulation; the concomitant use of aspirin, nonsteroidal anti-inflammatory agents, or other drugs that influence hemostasis; a history of bleeding; advanced age; a history of stroke; or the presence of serious comorbid conditions.[49] With an INR of 2.0 to 3.0, the annual risk of a major bleed is 1% to 3%.[45] Warfarin-induced skin necrosis is a rare complication that usually develops soon after warfarin therapy is initiated in patients with congenital or acquired protein C or protein S deficiency.[288] It likely results from the rapid decrease in levels of these anticoagulant proteins that precedes reduction in prothrombin levels. To circumvent this complication, patients with known protein C or protein S deficiency should be started on maintenance, rather than loading, doses of warfarin after therapeutic doses of heparin have been given.

Contraindications and Drug Interactions

Patients who have contraindications to anticoagulation therapy should not be given warfarin (see Box 22-1). Because warfarin is teratogenic, its use should be avoided, if possible, in pregnancy.[289] Numerous medications may influence patient response to warfarin.[290] Any change in medication profile, therefore, should prompt more frequent anticoagulant monitoring.

CONCLUSIONS AND FUTURE DIRECTIONS

A number of new anticoagulants with significant clinical potential have recently been evaluated in patients with acute coronary syndromes. Of these, only LMWH, fondaparinux, and bivalirudin have been introduced into practice. Despite

promising data, the role of the other agents in this patient population remains to be clearly delineated. The greatest unmet need in anticoagulation therapy is replacement of warfarin with an orally active agent that can be given in fixed doses without routine coagulation monitoring. Consequently, most of the current attention is focused on new oral anticoagulants. Those in the most advanced stages of development are the oral direct thrombin and factor Xa inhibitors. Dabigatran etexilate and rivaroxaban have been licensed for thromboprophylaxis in patients undergoing hip or knee replacement surgery in Europe and Canada. The results of the RELY trial with dabigatran highlight the promise of these new agents and their potential to replace warfarin for stroke prevention in patients with atrial fibrillation. The challenge for the future will be to determine which of the numerous agents currently under development will provide the greatest efficacy with the greatest degree of safety.

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CHAPTER 23

Beta Blockers, Calcium Channel Blockers, Ranolazine, Nitrates, and Nitric Oxide Donors: Use in Acute Coronary Syndromes

Patrick Commerford and Lionel H. Opie

The current focus of the management of the acute coronary syndromes (ACS) is on antithrombotic and antiplatelet agents and the selection and timing of revascularization procedures. With a few notable exceptions, use of beta blockers and calcium channel blockers (CCBs) and other agents to alleviate ischemia through other mechanisms have received little in the way of new scrutiny since preparation of this chapter in the previous edition of this book. Many recommendations are based on small studies which were performed prior to the widespread use of early revascularization, either percutaneous or by means of thrombolysis, and prior also to the availability of newer anticoagulants and oral and intravenous antiplatelet agents that have revolutionized the management of these conditions. It is also important to recognize that at the time many of the earlier studies were performed, therapeutic strategies subsequently shown to be harmful and hence abandoned were in use and may have confounded the interpretation of the results. For example in ISIS-1 more patients in the control arm were prescribed CCBs,[1] a practice now discouraged. The change that has occurred in the definition of the ACS also renders interpretation of the information difficult and extrapolation from older studies problematic.

Previously, the clinical syndromes of unstable angina and myocardial infarction were seen as distinct entities and often studied as such. It is now recognized that particularly in the early hours, when important therapeutic decisions have to be made, the distinctions may not be clear-cut. Rather they are part of a continuum and the diagnostic category of any single patient may change with time, the availability of repeated laboratory tests, or evolution of electrocardiographic changes. The integration of previous knowledge and experience with the beta blockers, CCBs, and other pharmacologic therapy into the modern management of the acute coronary syndromes is often not straightforward.

PHARMACOLOGIC PROPERTIES

Beta blockers act primarily by reducing myocardial oxygen demand, with negative chronotropic and inotropic effects that reduce heart rate, stroke volume, and blood pressure. A less well known metabolic effect of reducing blood free fatty acid levels improves metabolism of ischemic myocardium. Beta blockers also have antiarrhythmic effects as demonstrated by experimental studies showing an increase in ventricular fibrillation threshold and clinical trials showing a relative risk reduction in sudden cardiac death.[2] Prolonged diastole consequent on the bradycardia increases coronary diastolic blood flow and hence myocardial perfusion. Adverse remodeling may be reversed and left ventricular hemodynamic function improved by beta blocker administration in combination with other agents after myocardial infarction.[3,4]

Calcium channel blockers (CCBs) are all potent vasodilators. Reduced afterload reduces myocardial oxygen demand and coronary vasodilatation may increase supply. The non-dihydropyridines, verapamil and diltiazem, have negative inotropic effects and cause modest reductions in heart rate.

Nitrates act by forming nitric oxide within smooth muscle cells to stimulate the production of the vasodilator cyclic guanosine monophosphate (cGMP) via guanylate cyclase.[5] They exert their anti-ischemic effect through several different mechanisms. They are potent venodilators and peripheral venous pooling, reduced venous return, and reduction in ventricular volume with consequent reduction in ventricular wall stress reduces myocardial oxygen demand. Reduced aortic systolic pressure

provides a similar benefit. Reduction in left ventricular end-diastolic pressure improves the trans-myocardial perfusion gradient and subendocardial coronary perfusion improving myocardial oxygen supply. These peripheral effects may be more important than direct effects of dilating large coronary arteries and arterioles, relieving any epicardial coronary spasm or dynamic stenoses and dilatation of collaterals, which may have a direct effect on improving myocardial oxygen supply.

Ranolazine, unlike other agents discussed in this chapter, alleviates myocardial ischemia without clinically significant effects on heart rate or blood pressure.[6] It is considered to have two modes of action. First, it has been emphasized that it acts as a partial fatty acid oxidation inhibitor, similar to trimetazidine. Secondly, as more recently emphasized, it inhibits the late phase of the cardiac inward sodium current (I_{Na}) during repolarization. This current is more active during periods of myocardial ischemia, increasing intracellular sodium and hence calcium concentrations. Increased intracellular calcium may impair diastolic function and precipitate ventricular arrhythmias.

Properties of Beta Blockers

Beta blockers are sometimes divided into arbitrary generations. First-generation agents, such as propranolol, nonselectively block all the beta receptors ($beta_1$ and $beta_2$) Second-generation agents such as atenolol, metoprolol, acebutolol, bisoprolol and others, have relative selectivity when given in low doses for the $beta_1$ (largely cardiac) receptors. Third-generation agents have vasodilatory properties, acting through the following three mechanisms: (1) agents with added α-adrenergic blockade, as in the case of labetalol and carvedilol; (2) nitric oxide donation as in the case of nebivolol (see section on nitric oxide donors); and (3) a group now less used with added intrinsic sympathomimetic activity, including pindolol. Other nonvasodilatory beta blockers tend to promote systemic vascular and coronary vasoconstriction by unopposed α-adrenergic activity.

There are other marked differences between beta blockers in pharmacokinetic properties with widely varying half-lives and different lipid and water solubility. There is little compelling evidence that any of these properties confers significant therapeutic advantage. Simple clinical logic would favor the use of short-acting agents in the hemodynamically unpredictable ACS but paradoxically much of the available evidence of benefit is with longer acting agents.

Properties of Calcium Channel Blockers

CCBs are conventionally divided into the following: (1) predominantly vascular-active dihydropyridines (DHPs), of which nifedipine is an example of the first generation and amlodipine and felodipine are referred to as the second-generation; and (2) the more cardioactive non-DHPs, which are also called the *heart rate-slowing agents.* Both types of CCBs, but particularly the DHPs, inhibit the vascular long-lasting calcium channels to diminish calcium ion entry and to cause vasodilation. Another vascular action, well studied experimentally, is increased production of nitric oxide by the vascular endothelium, a process that can be expected to be protective by the vasodilatory and antiplatelet properties of nitric oxide. Verapamil and diltiazem have modest heart rate lowering effects and negative inotropic effects which when coupled to peripheral vasodilatation reduce myocardial oxygen consumption. With the DHPs, particularly short-acting nifedipine, the more marked peripheral vasodilatation stimulates adrenergic reflexes and tachycardia, which could account for the adverse effects of nifedipine capsules in the ACS.

BETA BLOCKERS IN CLINICAL PRACTICE IN ACUTE CORONARY SYNDROMES

Beta Blockers in ST-Elevation Acute Coronary Syndromes

The overall evidence for the benefits of beta blocker treatment in reducing morbidity and mortality is considered to be best for patients with ST-segment elevation myocardial infarction (STEMI). A comprehensive systematic review and meta regression analysis published in 1999 identified a 29% reduction in the odds of death in long-term trials with a relatively modest 4% reduction in the short-term trials.[7] The mortality benefit is in part due to a lower rate of sudden cardiac death. Beta blocker prescription remains a primary recommendation in most guidelines for the management of patients after myocardial infarction.[8,9] The contemporary evidence base and practical considerations involved in implementation of beta blocker therapy after infarction have been comprehensively reviewed.[10] Many of the key studies on which the recommendations are based were performed in the era prior to routine administration of antiplatelet agents, thrombolysis, and primary percutaneous coronary intervention (PCI). The evidence that beta blockers confer benefit after myocardial infarction has been considered to be so good that their prescription within 7 days of hospital discharge has been used as a marker of quality of care. This practice is now so well-accepted and implementation so widespread that it no longer is useful as such a marker.[11]

Despite the favorable findings of the earlier studies and widespread use later after the onset of infarction in the convalescent stage, the key following questions remain:

1. What is the role of early intravenous administration of beta blocker?
2. Do patients undergoing primary percutaneous intervention benefit from beta blocker therapy?
3. What is the role of beta blockers in the face of heart failure early after myocardial infarction (MI)?
4. Should the traditional contraindications to beta blocker therapy still be applied to patients after STEMI?
5. If the data on early oral beta blockade are indeed applicable to current practice, what is the agent of choice and in which dose?

Early Administration of Beta Blockers. The early treatment of patients with suspected acute myocardial infarction with intravenous followed by oral beta-blockade was studied in many trials in the 1980s (Table 23-1). Overall, the results of these studies have been interpreted as indicating that the treatment is safe and moderately effective in a group of relatively low-risk patients, preventing six deaths per thousand patients treated (ISIS-1).[1] There has been persistent uncertainty about the addition of early beta blocker therapy, particularly intravenous therapy, to standard treatment; opinions differ[12,13] and practice varies widely.[14] There has been no large trial testing the effects of early oral beta blockade versus placebo (see Table 23-1).

COMMIT Trial. Those considerations prompted the conduct of the COMMIT trial, which randomized 45,852 patients within 24 hours of onset of symptoms to intravenous and continued oral metoprolol or placebo.[15]

The majority of patients had STEMI or left bundle branch block and approximately half received thrombolytic therapy. Patients with "moderate" heart failure were allowed to be enrolled and 20% were estimated to be in Killip class II and 5% in class III at entry. Prior beta blocker use was not an exclusion. Up to 15 mg of metoprolol was administered intravenously in 5-mg aliquots at 2- to 3-minute intervals provided the heart rate was above 50 beats/min and systolic blood pressure above 90 mm Hg. Following this, 50 mg of metoprolol was administered orally and repeated every 6 hours for the first day followed by 200 mg in sustained-release formulation daily thereafter.

TABLE 23–1 Trial Outcome Data on Use of Beta Blockade in Acute Coronary Syndromes*

Trial (Date)	Entry Criteria	Drug and Dose	Outcome
Ryden (1983)[62]	1395 patients with suspected or later proven MI	Metoprolol 15 mg IV (3 × 5 mg), then 100 mg every 12 h for 3 months	Less ventricular fibrillation ($P < .05$)
Norris (1984)[63]	735 patients with suspected MI within 4 h of onset	Propranolol 7 mg IV over 5 min (weight adjusted); oral 40 mg 1, 3, 7, 11, 15, 19, 23, 27 h (after start)	Less ventricular fibrillation ($P = .006$)
MIAMI (1985)[64]	5778 patients with definite or suspected acute MI	Metoprolol 15 mg IV (3 × 5 mg), then 100 mg every 12 h until day 16	No overall difference, but in high-risk group (retrospective) 29% fall in deaths
ISIS-1 (1986)[1]	16,027 patients within 12 h of onset of suspected MI	Atenolol 5-10 mg IV at once, then 100 mg/day orally for 7 days	Vascular mortality on first day reduced, $P < .003$; days 1-365, $P < .01$
HINT (1986)[35]	338 patients with unstable angina	Metoprolol, 100 mg twice a day	MI at 48 h; odds ratio 1.07 (95% CI 0.54-2.09)
Kirshenbaum (1988)[65]	16 patients with acute MI or unstable angina with wedge pressure 15-25 mm Hg	Esmolol up to 300 μg/kg/min IV up to 48 h	Rate pressure product fell, wedge pressure the same, drug effect over by 30 min. In 4 of 16, drug stopped (oliguria, hypotension)
Roberts TIMI II-B (1991)[19]	1434 patients; beta blockade given early as IV then oral to 720, deferred for 6 days in 714 patients; all t-PA early	Early: Metoprolol 15 mg IV (3 × mg), then 100 mg in first 12 h, then 200 mg/day in split doses; Deferred: on day 6, start 50 mg then 100 mg, both twice daily	Mortality and ejection fraction at discharge unchanged; less early reinfarction and recurrent pain in early group; trend toward fewer intracranial bleeds
Van de Werf (1993)[66]	292 patients with acute MI ≤5 h duration (divided atenolol, placebo, alinidine)	Atenolol group: 5-10 mg IV then 25 to 50 mg twice daily	No clinical differences except 6% nonfatal pulmonary edema in atenolol vs. 0% in placebo group
COMMIT (2005)[15]	45,852 patients within 24 h of suspected MI; note metoprolol CV effects heterogeneous	Metoprolol up to 15 mg IV then 200 mg/day orally for mean of 15 days	Mortality equal (7.7%); per 1000 treated, 5 less reinfarction and 5 less ventricular fibrillation, versus 11 more cardiogenic shock

All doses oral except for IV (intravenous); *All except HINT are suspected or proved early-phase clinical acute myocardial infarction.

In this, the largest trial of early intravenous beta-blockade in acute myocardial infarction neither of the co-primary outcomes of (1) death or (2) a composite of death, reinfarction or cardiac arrest, were reduced by allocation to metoprolol. For every thousand patients on treatment for a mean of 15 days, metoprolol was associated with one fewer deaths (7.7% vs. 7.8%), five fewer reinfarctions, and five fewer episodes of ventricular fibrillation. This was counterbalanced by increased cardiogenic shock, heart failure, persistent hypotension and bradycardia (in total 88 serious adverse events). Shock occurred most frequently during the first 24 hours of treatment and rates of cardiogenic shock were greater for those older than 70 years of age, with systolic blood pressure less than 120 mm Hg, with a heart rate of greater than 110 beats/min, or with any heart failure. The authors pointed out that it was not possible to identify reliably any particular category of patients in which the beneficial effects of early beta blocker therapy clearly outweighed the adverse effects, although there was a tendency toward net benefit in those at lower risk of developing shock. The effects were time-dependent and in contrast with the early risk of cardiogenic shock, the reductions in the risk of reinfarction and of ventricular fibrillation emerged more gradually. The overall net effect of metoprolol on the combined efficacy and safety outcome changed from being significantly adverse during days 0 and 1 to being significantly beneficial thereafter.

The results of this very large placebo-controlled, double-blind investigation and the observational analysis of GUSTO-I[13] have led to suggestions that early intravenous beta-blockade should be removed from standard recommendations and replaced by the introduction of a beta blocker only once hemodynamic stability is ensured[9,16] This is despite contemporary experimental evidence showing that intravenous beta blocker reduces infarct size.[17]

However, it can be argued that the outcome of COMMIT does not justify all the conclusions that have been drawn and that some aspects of the trial are open to criticism. In COMMIT, high doses of both intravenous and oral metoprolol were given to all patients including some with heart failure and others already on treatment with a beta blocker. These patient characteristics and the policy of continued administration of intravenous beta blocker provided systolic blood pressure was not lower than 90 mm Hg and heart rate was above 50 beats/min may have led to harm and the consequent inability to demonstrate benefit. Prudent clinical practice is not to administer intravenous beta blockers to patients with STEMI who have clinical heart failure, extreme bradycardia, or hypotension nor to those already on treatment with beta blockers. Guidelines for both STEMI[9] and non–ST-elevation myocardial infarction (NSTEMI)[8,18] advise against acute use of beta blockers in patients with rales or an S3 gallop and most clinicians would avoid intravenous administration of beta blockers to patients in pulmonary edema (Killip III). The most recent guidelines for the management of STEMI continue to emphasize the importance of attempting to introduce beta blocker therapy as early as possible.[9] However, in the only study comparing early intravenous beta blockade at a mean delay of 3.3 hours after the onset with later oral administration at 6 days, there were no substantial differences in mortality at 1 year, although early reinfarction and recurrent chest pain were reduced.[19] Hence the guidelines do not recommend routine intravenous administration, while emphasizing the great importance of carefully screening patients for contraindications to beta blockade before its introduction, the necessity of continued monitoring of patients for complications, and careful and prudent dose titration.[8,9,18] The use of ultra-short-acting beta blockers such as esmolol is attractive[20] but has also not been tested in large-scale outcome trials and has not achieved widespread clinical implementation.

Primary Percutaneous Coronary Intervention (PCI) and Beta Blockade. The excellent results of primary PCI have made it the treatment of choice for patients with STEMI-ACS when patients are seen early and the necessary personnel and facilities are available. The necessary urgency in obtaining shortened "door-to-balloon" times may mean that potentially beneficial therapies not directly linked to PCI are inadvertently omitted. Additionally the shortened hospitalization times and perception of both physician and patient that the condition has been cured may lead to omission of important prophylactic therapies. While there is no good evidence from prospective randomized trials of whether or not beta blocker therapy is beneficial in the setting of primary PCI for STEMI, observational analyses suggest that it is and should be administered intravenously before PCI and continued orally after the procedure.[21] Retrospective analysis of the CADILLAC trial of primary PCI showed that 30 mortality was reduced from 2.8% to 1.5% by pre-procedural administration of intravenous beta blockade and improvement in left ventricular function between baseline and 7 months was greater after intravenous beta blockade.[22] These benefits were limited to patients not being treated with beta blockers prior to infarction. Pre-procedural beta blockers may protect patients undergoing primary PCI against ventricular tachycardia and ventricular fibrillation during the procedure.[23] Beta blockade after successful primary PCI reduced 6-month mortality from 6.6% to 2.2% in observational studies.[24] The greatest benefit was seen in patients with low ejection fraction or multi-vessel disease. These observational studies suggest that the advent of a new and effective form of treatment for STEMI is a stimulus to fully investigate the combination with beta blockade to obtain maximum patient benefit in appropriately selected patients.

Beta Blockade and STEMI-Related Left Ventricular Dysfunction and Heart Failure. The beneficial effects of beta blockers after STEMI in the trials of an earlier era (see Table 23-1) were shown well before the introduction of current standards of reperfusion, and also before the benefit of the angiotensin converting enzyme inhibitors (ACE-Is) in heart failure and left ventricular dysfunction, and the marked benefits of beta blocker therapy in chronic heart failure were established. Many patients with heart failure or asymptomatic left ventricular dysfunction were almost certainly excluded by cautious physicians evaluating beta blockers after STEMI in the early trials. Three retrospective analyses—SAVE, SOLVD, and AIRE[25-27]—showed that patients treated with a beta blocker had lower rates of events than those not so treated and indicate that beta blockers can and should be used in patients with treated heart failure and left ventricular dysfunction after STEMI. The results of the CAPRICORN trial reinforce this opinion.[28] This investigation randomized patients with reduced ejection fraction (<40%) within 21 days after myocardial infarction who were treated with an ACE-I to carvedilol in increasing dose or placebo. Carvedilol reduced all-cause mortality and nonfatal infarction. The all-cause mortality rate was 12% on carvedilol versus 15% on placebo at an average follow-up of 1.3 years. Approximately half of all participants had experienced reperfusion with thrombolytics or primary PCI. The effects were seen early and the carvedilol group experienced a reduction in mortality in the first 30 days, which is the period of greatest risk for recurrent infarction, sudden death, and all-cause mortality.[29] The effects within the first 30 days were similar in direction and magnitude to those observed during the prolonged follow-up period.

Guidelines recommend early introduction and continued treatment with beta blockers for all patients without contraindications after STEMI[9] But concern remains that they are underused, particularly in patients with heart failure.[30,31] This may reflect physicians' concerns that these agents may worsen heart failure. The results of CAPRICORN should allay these fears and encourage more widespread use of beta blockers in addition to all other appropriate therapy for heart failure after MI. Beta blockers can worsen heart failure and are generally considered contraindicated in hemodynamically unstable patients. Specific agents, such as carvedilol, when used appropriately with careful up-titration of dose in addition to other appropriate treatment in stable patients in the convalescent phase of MI, are safe and confer benefit. The only side effect found during up-titration of carvedilol started in the convalescent phase was hypotension necessitating withdrawal in some patients.

Relative contraindications and potential harmful effects in some groups of patients are often cited by clinicians as reasons not to prescribe beta blockers after STEMI and may be responsible for under-use and under-dosing. Survival benefit with beta blocker therapy has been demonstrated in observational registry analyses of large numbers of patients after MI with such relative contraindications as chronic lung disease, diabetes, peripheral vascular disease, as well as heart failure and left ventricular dysfunction.[32]

Where cocaine use is considered a possible precipitant of STEMI, beta blocker therapy is generally considered to be contraindicated.[33]

Beta Blockers in Non–ST-Elevation Acute Coronary Syndromes

In contrast to the situation in patients with STEMI where there is a considerable reported experience with beta blockers and fair evidence of benefit in trials from an earlier era, there is a remarkable lack of good information from randomized trials on the use of these agents in patients with unstable angina and NSTEMI. Despite the lack of contemporary published evidence of benefit, oral beta blockers are recommended to be started early in the absence of contraindications in current guidelines and intravenous administration is advised in patients with ongoing rest pain, especially with tachycardia or hypertension.[8,18]

Observational data suggest that acute beta blockade, given within 24 hours of onset, but not specifically intravenously, is underused especially in the elderly and in those with heart failure.[34] These recommendations are based on expert opinion, clinical experience[34] and old, small, and inconclusive studies that would be unlikely to survive the careful scrutiny to which current therapies are subjected. The HINT trial, published two decades ago, was the largest study evaluating beta blockers in NSTEMI.[35] In that study 338 patients, not previously treated with a beta blocker, were randomized to placebo, nifedipine, or metoprolol. Metoprolol-treated patients experienced fewer ischemic events but the effect was not statistically significant. A more recent but smaller study evaluated carvedilol compared to placebo in addition to aspirin, nitrates, and heparin. Carvedilol reduced the number and duration of ischemic episodes and the number of patients experiencing ischemic episodes during 48 hours of ambulatory monitoring.[36] The clinical relevance of this benefit is unclear. The totality of evidence of benefit for beta blocker therapy in NSTEMI-ACS is far from convincing. A dated review of double-blind randomized trials in patients considered to have threatening or evolving myocardial infarction suggests that such therapy offers an approximately 13% reduction in the risk of progression to myocardial infarction.[37]

Some good observational evidence that is available to guide practice in the current era comes from the analysis of results of several trials of a variety of antiplatelet agents in patients with ACS who were undergoing percutaneous intervention.[38] After 1 month, there were more deaths (2%) in patients not receiving beta blocker therapy than in those treated with beta blockers (0.6%). This mortality benefit persisted to 6 months by which time 3.7% of patients not treated

with beta blockers versus 1.7% of those treated with beta blockers had died. Current practice as evaluated in large registries indicates that beta blockers are used in the majority of patients within the first 24 hours of presentation with symptoms of NSTEMI.[39] Such use is correlated with both lower in-hospital mortality and lower mortality at 6 months. Failure to institute beta blockade within the first 24 hours was associated with lower rates of subsequent beta blocker therapy and the use of evidence-based therapies.

Analysis of beta blocker use in usual practice in a very large registry of 72,054 patients with NSTEMI at 509 U.S. hospitals between 2001 and 2004 showed that acute beta blocker use, implemented in more than 80% of such patients, was associated with lower in-hospital mortality (3.9% vs. 6.9%, $P < .001$) and the beneficial effects were seen in patients with and without signs of heart failure.[34] The authors concluded that the majority of NSTEMI patients in usual practice receive acute beta blocker therapy, but some subgroups remain undertreated. Given the improved clinical outcomes in nearly all subgroups assessed, broader use in such patients appears warranted, albeit lacking prospective trial evidence. A similar frequent use of beta blockers in international practice is reflected in an early review[40] and in the GRACE registry.[41]

Thus, the overall evidence base for the use of beta blockers in patients with unstable angina or NSTEMI, in contrast to much other evidence on which important therapeutic decisions are based in cardiology, is virtually nonexistent apart from registry studies. Yet almost all guidelines advise the use of beta blockers. Given the demonstrated benefit of long-term beta blockade after MI and the excellent symptomatic relief they provide in patients with stable angina, it is unlikely that the current recommendations will be tested in any randomized trial and will remain standard in patients without major contraindications.

CALCIUM CHANNEL BLOCKERS IN CLINICAL PRACTICE IN ACUTE CORONARY SYNDROMES

Calcium channel blocking agents (CCBs) were originally developed as anti-ischemic agents and were suggested for use in acute coronary syndromes when it was considered they would limit the extent of myocardial necrosis.[42] Their potent vasodilatory properties seemed logical therapy some decades ago when coronary spasm was considered to be important in the pathogenesis of ACS.[43,44] The current understanding is that coronary vasospasm is not central to the pathogenesis of the ACS. These agents have undoubted anti-ischemic properties[45] and may be appropriately used to relieve symptoms when other therapy is contraindicated. However in the setting of the ACS, there is no evidence that they offer anything other than symptomatic benefit and concerns remain about their safety. It is unclear why clinical outcomes are not consonant with expectations based on experimental results. It may be that unlike the beta blockers, which share the universal quality of beta blockade that serves to lower the heart rate and thus myocardial oxygen consumption (crucial in the acute coronary syndromes), the CCBs do not have consistent effects on heart rate. Some increase heart rate by reflex adrenergic effects consequent on vasodilatation and those that do lower the heart rate by virtue of action on the sinus node have at best a modest impact on heart rate, considerably less than that of beta blockers, and unfortunately also have negative inotropic effects.

The limited information available from trials of the early use of CCBs in NSTEMI-ACS is summarized in Table 23-2. It is limited, incomplete, and there is no evidence of benefit. Consequently most major guidelines on the management of NSTEMI-ACS/unstable angina pectoris (UAP) advise against the use of CCBs as first-line agents and recommend that they should only be used for control of symptoms which persist after beta blockers have been administered or if beta blockers are contraindicated.[34]

Short-acting nifedipine was demonstrated to be harmful and to increase mortality in a very early study of ACS[35] although when combined with metoprolol it gave significant outcome benefit that metoprolol alone did not. There has been no follow-up to provide supporting data favoring the nifedipine-metoprolol combination, so the general recommendation is that short-acting nifedipine should be avoided. Potent vasodilatation, hypotension, and reflex sympathetic activation may be the underlying mechanisms of harm.

The nondihydropyridine CCBs verapamil and diltiazem slow heart rate and thus theoretically appear more attractive in patients with ACS, but have not been shown to be any better than placebo. In unstable angina, intravenous diltiazem gave better outcomes over 1 year than did intravenous nitroglycerin.[46,47] Event-free survival was reduced (34.4% vs. 45%, $P < .04$). However, this is a small trial that needs repetition. In an observational study, long-term diltiazem use after unstable angina was associated with a nonsignificant increase in the adjusted death rate and risk of re-hospitalization or death when compared with beta blockade.[48] In NSTEMI, oral diltiazem started between 24 and 72 hours of onset of

TABLE 23–2 Trial Outcome Data on Use of Calcium Channel Blockers in Acute Coronary Syndromes Including Unstable Angina

Trial	Entry Criteria	Drug and Dose	Outcome
DAVIT 1 (1984)[67]	3498 patients with clinical acute MI admitted to CCU	Verapamil 0.1 mg/kg IV and 120 mg orally followed by 120 mg thrice daily for 6 months	No effect on mortality or reinfarction at 6 months
HINT (1986)[35]	515 patients with unstable angina	Nifedipine 10 mg every 4 h; with metoprolol 200 mg daily or placebo	Nifedipine-only group: clinical MI doubled at 48 h; for nifedipine added to prior metoprolol, MI 48 h reduced; OR 0.56 (CI 0.30-0.99)
Göbel (1995)[46]	129 patients with unstable angina	Diltiazem 25 mg IV over 5 min, then 5-15 mg/h to maximum 25 mg/h vs. nitroglycerin infused over 48 h	Reduced refractory angina in diltiazem group; fewer events over 1 year of follow-up
DATA (1998)[68]	59 patients with early-phase acute MI and ST-segment elevation treated with t-PA	Diltiazem IV 10 mg bolus, then 10 mg/h for 48 h, then oral up to 4 wk	Composite end point of death, reinfarction, and recurrent ischemia reduced by 78% at 35 days ($P = .027$)
Theroux (1985)[69]	100 patients with unstable angina	Diltiazem up to 120 mg thrice daily or propranolol up to 80 mg thrice daily	No difference in outcome with regard to symptoms, reinfarction, or death

symptoms and continued for 14 days reduced reinfarction or severe angina.[49] A much larger study evaluated diltiazem (240 mg/day) against placebo in patients in the first 2 weeks after STEMI or NSTEM.[50] Treatment did not reduce mortality during a mean follow-up of 25 months. Diltiazem reduced cardiac events in a subgroup of patients with preserved left ventricular function and increased the cardiac event rates and cardiac mortality in patients with impaired left ventricular function. Diltiazem offered no benefit when added to treatment of patients with STEMI who had received thrombolysis.[51]

Verapamil when tested in a dose of 360 mg/day given late (1 week) after admission in patients with acute myocardial infarction nonsignificantly reduced total mortality and cardiac events.[52] Benefit was confined to patients without heart failure. An overview of the post-infarction trials suggested that diltiazem and verapamil reduced the risk of reinfarction but probably not mortality compared with placebo when added to standard therapy.[53]

The relevance of the results of these studies to contemporary practice is questionable. Very few patients are still in hospital and receiving new medications a week after myocardial infarction. All the emphasis of current treatment strategies of the ACS is on very early management (within hours of presentation); there seems to be no place in the available evidence for the use of CCBs in this situation. Calcium channel blockers (diltiazem by choice) should be reserved for relief of symptoms in the occasional patient in whom beta blockers are contraindicated. When used for other indications such as control of blood pressure in these situations, it is reasonable (but without supporting outcome data) to use newer agents (amlodipine, felodipine) preferably after beta blockers have been introduced to prevent reflex tachycardia.

NITRATES IN ACUTE CORONARY SYNDROMES

Sublingual or buccal nitroglycerin is commonly administered as emergency treatment for patients presenting to the emergency room or a primary care physician with a chest pain syndrome considered to be due to cardiac ischemia. The usual recommendation is that in the absence of contraindications the dose should be repeated three times at 5-minute intervals if symptoms continue. The arguments behind this well-established practice are that such use of nitrates relieves symptoms, lowers afterload, reduces pulmonary congestion if present, and reverses vasospasm in those uncommon patients in whom this may be etiologically important. The response to short-acting nitrates may also be diagnostically helpful. Before administration patients should be questioned about prior use of phosphodiesterase-5 inhibitors. Nitrate administration may induce severe hypotension if administered within 24 hours of sildenafil use (and probably longer with longer acting compounds).

Although intravenous nitrates are standard therapy in unstable angina, there are no studies on their use in current clinical practice. They are given for pain relief or control of blood pressure, and clinical experience indicates that they are effective in attaining those aims. There are no contemporary studies showing any outcome benefit. Among the very few early studies, intravenous nitrates were less effective than diltiazem, both when given acutely[46] and when followed up a year later.[47]

Intravenous nitroglycerin (discontinued in the U.S.) is usually started at 5 to 10 μg/minute, which can be up-titrated to 200 μg/minute or, occasionally to 1000 μg/minute, depending on the clinical course and aiming at relief of pain. An alternate aim, besides relief of pain, is to reduce mean blood pressure by 10%. The infusion can be maintained for up to 36 hours. Note that nitroglycerin is readily absorbed (40% to 80%) by PVC tubing, but not onto polyethylene or glass. Nitrostat infusion sets use nonabsorbent materials, so that the calculated dose is in fact delivered to the patient.

An alternate is intravenous isosorbide dinitrate (not licensed in the United States). Nitrate patches and nitroglycerin ointment should not be used. Apart from initial emergency or first-contact administration as outlined above, there is no place for intermittent nitrate therapy in this condition and any nitrate tolerance has to be overcome by increasing the nitrate dose.

RANOLAZINE IN ACUTE CORONARY SYNDROMES

Ranolazine reduces anginal frequency and improves effort tolerance in patients with chronic stable angina. Its novel mechanism of action and lack of deleterious hemodynamic effects make it an attractive therapeutic option in patients presenting with an ACS. The MERLIN study randomized 6560 patients presenting within 48 hours of onset of symptoms of NSTEMI to intravenous followed by oral ranolazine or placebo in addition to conventional treatment.[54] Treatment with ranolazine did not reduce the primary efficacy endpoint, a composite of cardiovascular death, MI, or recurrent ischemia during a year of treatment. Additional analysis revealed a 13% relative reduction in the risk of developing recurrent ischemia and a lesser requirement for increases in other antianginal therapy in patients treated with ranolazine. Ranolazine was safe, with no increase in symptomatic documented arrhythmias during continuous electrocardiographic recording. For the first 7 days after randomization, ranolazine treated patients had significantly fewer episodes of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses.[55] In the subgroup of patients (n = 3565) with prior chronic angina, the benefits were the same as in the whole group, but there was better exercise performance after 8 months.[56] These results probably mean that in practice this agent could pragmatically be used as add-on therapy in NSTEMI patients who remain symptomatic despite otherwise optimal antianginal treatment and in whom no revascularization strategy is feasible.

Trimetazidine, an agent with some properties similar to ranolazine, did not reduce mortality compared to placebo when administered as an intravenous bolus prior to or at the time of thrombolysis, followed by an intravenous infusion for 48 hours in patients with STEMI.[57]

NITRIC OXIDE DONORS

As reviewed in the previous edition of this book, nitric oxide donors have theoretical, but not proven use in the ACS and, as in other areas of vascular disease, have not achieved the therapeutic potential promised.[58,59] Potentially the most interesting new compound is nebivolol, a beta-1 selective blocker with nitric oxide donation as one of its mechanisms of action. The nitric oxide donor component leads to vasodilation, thought to be mediated by increased vascular NO synthase activity.[60] Nebivolol has been tested in only one outcome study in elderly patients with heart failure, SENIORS, in which it reduced the combined end point of hospitalization and death, but mortality did not decrease significantly.[61] Although there have been no studies on nebivolol and unstable angina, this clearly would be the most interesting beta blocker to study, especially as there are no good existing studies on beta blockade in acute coronary syndromes in the era of present clinical practice.

SUMMARY

In contrast to developments in treatment strategies directed at alleviating the "supply-side" of the myocardial oxygen imbalance underlying the ACS, there has been disappointingly little progress in the development of therapies directed at the "demand side" of the equation. A major new trial has forced re-examination of how intravenous beta blockers are used in acute myocardial infarction. Guidelines now emphasize the importance of using oral beta blockade in as many patients as possible, with the stress on dose titration and careful patient evaluation to ensure contraindications to their use do not exist. There have been no major advances in our understanding of the use of nitrates, used to treat pain and reduce blood pressure, and CCBs in this clinical setting. The metabolic modulators such as ranolazine have an ancillary protective role in non-ST EMI, while the nitric oxide donating beta blocker nebivolol remains to be tested in acute coronary syndromes.

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CHAPTER 24

Adenosine Triphosphate–Sensitive Potassium Channels, Adenosine, and Preconditioning

Fabrizio Tomai and Leonardo De Luca

Ischemic preconditioning refers to the ability of short periods of ischemia to make the myocardium more resistant to a subsequent ischemic insult. This term was introduced for the first time by Murry and coworkers, who found in a canine model that four consecutive periods of coronary occlusion of 5 minutes were able to reduce the infarct size caused by a subsequent period of occlusion of 40 minutes by as much as 75%.[1] This classic form of ischemic preconditioning has now been observed in several animal species.[2]

Although ischemic preconditioning initially referred to the ability of short periods of ischemia to limit infarct size,[1] some investigators extended this definition to include a beneficial effect on ischemia- and reperfusion-induced arrhythmias[3] and on myocardial stunning.[4] It is controversial, however, whether the reduction in the incidence of arrhythmias by ischemic preconditioning is due to a direct antiarrhythmic effect or whether it is a mere consequence of the delay of ischemic cell death.[1,3] Regarding the beneficial effects of ischemic preconditioning on postischemic contractile dysfunction, Cohen and colleagues[4] showed that in rabbits preconditioning can lead to enhanced recovery of contractile function of the myocardial region at risk. In this case also, the beneficial effects of preconditioning on acute recovery of contractile function might be a consequence of the delay of ischemic cell death; indeed, parameters of necrosis extent, i.e., infarct size and enzyme leakage, correlate with the enhancement of functional recovery.[4]

The chain of events that confers resistance to ischemia is only partially understood. Downey and coworkers[5] have developed the hypothesis that binding of surface receptors by agonists (including adenosine, bradykinin, opioids, acetylcholine, catecholamines, and oxygen radicals) results in the activation of protein kinase C (PKC). This appears to be the first element of a complex kinase cascade that ultimately causes opening of mitochondrial adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel, which may be a trigger and mediator, end-effector, or both, for ischemic preconditioning.[5,6] How the opening of mitochondrial K_{ATP} channel may be protective, however, is still uncertain. The following three hypotheses have been proposed: (1) mitochondrial swelling and optimization of respiration; (2) a decrease in the extent of mitochondrial calcium overload; and (3) stimulation of mitochondrial reactive oxygen species production.[7] Figure 24-1 is a diagram showing the proposed mechanism of preconditioning at the cellular level.

It is now well established that the protective effects of preconditioning are transient and last for less than 2 hours.[2,5] However, a so-called *second window of protection* or *delayed* ischemic preconditioning has been shown in different species, occurring 24 hours after the preconditioning stimulus and lasting for about 48 hours.[8,9] This time course is consistent with the concept that the second window of protection is mediated by the activation of genes encoding for cytoprotective proteins.[8,9] Similarly to the early phase of preconditioning, aside from a delayed anti-infarct effect, a delayed antiarrhythmic effect following preconditioning has been reported.[10] Furthermore, Bolli's group[11] has described a delayed preconditioning against myocardial stunning, independent of ischemic necrosis since the ischemic challenge utilized was insufficient to induce infarction.

EVIDENCE FOR PRECONDITIONING IN HUMAN MYOCARDIUM

Ischemic preconditioning represents the most powerful form of protection against experimental myocardial infarction (MI) described to date.[2,5] Indeed, this endogenous form of myocardial protection has been shown in all animal species investigated.[2,5] It seems, therefore, reasonable to assume that such a form of endogenous cardioprotection might also occur in the clinical setting. If this were the case, the possibility of exploiting this endogenous form of protection by pharmacologic means would be of great importance in the

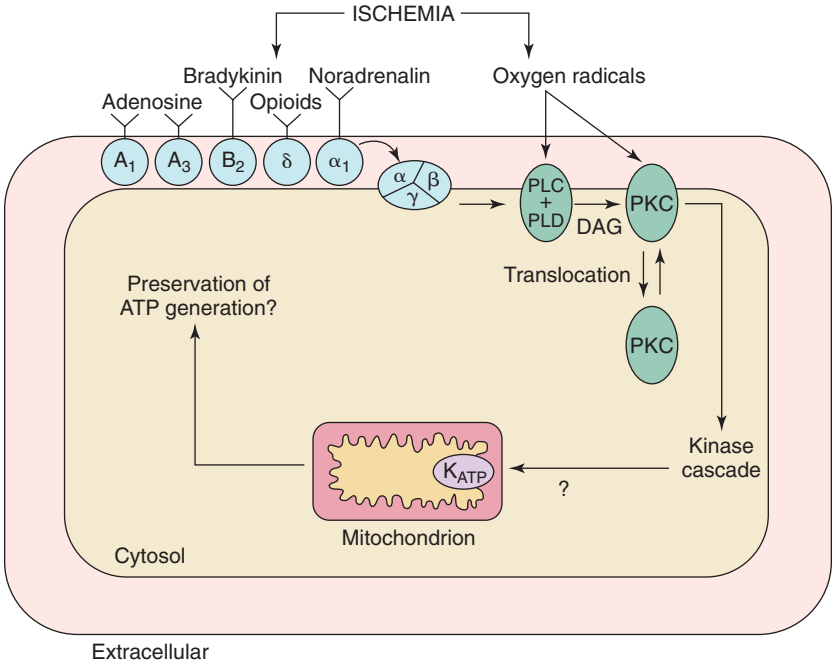

FIGURE 24–1 Diagram showing the proposed mechanism of preconditioning at the cellular level. Ischemia leads to release of adenosine, bradykinin, opioids, noradrenalin, and free radicals that together produce stimulation of phospholipase C (PLC) and/or D (PLD) that, in turn, activate protein kinase C (PKC). This appears to be the first element of a complex kinase cascade that ultimately causes opening of mitochondrial ATP-sensitive potassium (K_{ATP}) channel, which may be the final mediator of protection for ischemic preconditioning.

attempt to reduce myocardial infarct size. However, experimental findings on ischemic preconditioning cannot be directly extrapolated to humans. In fact, for both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on preconditioning in which infarct size is the end point. Thus, surrogate end points have been used, including contractile function, electrocardiographic ischemic changes, or biochemical evidence of cell damage. This has to be taken into account in the evaluation of clinical studies on preconditioning, as the mechanisms of such nonclassic forms of ischemic preconditioning may differ from those involved in the reduction of infarct size in the experimental models. Another important limitation of several published clinical studies is represented by the extent of coronary collateral flow, which, in humans, is a major determinant of the severity of myocardial ischemia during coronary occlusion; it cannot always be accurately quantified. However, in vitro human studies, in which confounding effects due to coronary collateral flow can be overcome, have shown that human cardiomyocytes can be preconditioned.[12-15] Carr and his co-workers[12] showed that isolated superfused isometrically contracting human atrial trabeculae can be preconditioned against a combined hypoxic and substrate depletion challenge by simulated ischemia and by A_1 and A_3 adenosine receptor activation. The same group has also demonstrated that protection against contractile dysfunction caused by a combined hypoxic and substrate depletion challenge can be induced by activation of PKC and by the opening of K_{ATP} channels and that the protection induced by PKC activation and preconditioning can be blocked by blockade of K_{ATP} channels.[13] Indeed, Cleveland and coworkers[14] have shown that in this model there is not evidence of any protection when the myocardium is obtained from diabetic patients exposed to long-term oral hypoglycemic agents, thus suggesting important clinical implications. Finally, Morris and Yellon[15] have shown in human atrial trabeculae that angiotensin-converting enzyme inhibitors can potentiate the protective effects of a subthreshold preconditioning stimulus, possibly due to bradykinin degradation inhibition resulting in enhanced B_2 bradykinin receptor activation. Such a demonstration may help to explain the mechanisms involved in the reduction of fatal ischemic events in patients treated with angiotensin-converting enzyme inhibitors.[16-19]

The limitations of the model of isolated superfused isometrically contracting human atrial trabeculae are the use of hypoxia rather than ischemia to initiate protection, of recovery of contractile function as surrogate end point, and of atrial rather than ventricular tissue. Finally, in vitro human studies do not provide answers about the clinical situations in which preconditioning does indeed occur nor clarify which mechanisms are involved in mediating ischemic preconditioning in different clinical settings. Thus, ischemic preconditioning in humans has been studied in the following clinical settings: (1) preinfarction angina; (2) exercise-induced ischemia (warm-up phenomenon); (3) coronary angioplasty; and (4) cardiac surgery.[20-23]

Preinfarction Angina

Some studies have shown that patients with MI preceded by angina have smaller infarcts and a better in-hospital outcome after thrombolytic therapy than patients without preinfarction angina.[24-26] At least three of the following mechanisms may explain this difference between infarctions that are preceded by angina and those that are not: (1) coronary collaterals; (2) reperfusion rate; and (3) ischemic preconditioning. Kloner and associates[24] found that patients with angina within 48 hours of MI had a lower in-hospital death rate and a smaller infarct size than patients without angina, despite a similar development of coronary collateral vessels assessed at angiography 90 minutes after MI, suggesting that preconditioning by pre-infarction angina might render the myocardium more resistant to infarction from the subsequent prolonged ischemic episode. Another attractive hypothesis about the protective role of preinfarction angina has been suggested by Andreotti and colleagues.[25] They compared the

infarct size of patients with or without unstable angina during the week before MI, taking into account also the speed of recanalization. Interestingly, in patients with preinfarction angina, as compared with those without, thrombolytic therapy resulted in more rapid reperfusion and smaller infarcts, suggesting that the benefit of preinfarction angina on infarct size might depend on a speedier coronary thrombolysis in addition to, or perhaps, instead of preconditioning. Also in this study there was no significant difference in collateral development between patients with and without preinfarction angina, implying that it is unlikely collaterals play a major role in explaining the beneficial effects of preinfarction angina. Ishihara and coworkersl[26] confirmed that reperfusion was more frequently achieved in patients with prodromal angina in the 24 hours before infarction, rather than in those without, suggesting a more efficient response of the infarct-related artery to thrombolytic therapy in the former. However, they also demonstrated that prodromal angina in the 24 hours before infarction, but not angina occurring at an earlier time, was independently associated to a better 5-year outcome, suggesting a role for ischemic preconditioning.

The Warm-up Phenomenon

The warm-up phenomenon, that is, the improved performance exhibited by more than half of patients with coronary artery disease following a first exercise test,[27,28] may be another clinical correlate of ischemic preconditioning. Okazaki and colleagues[27] demonstrated that in patients with a single lesion of the left anterior descending coronary artery, great cardiac vein flow is similar during the first and second exercise stress test, thus suggesting that the warm-up phenomenon is not accompanied by an increase in total myocardial blood flow. Interestingly, myocardial oxygen consumption was reduced during the second test, suggesting increased metabolic efficiency, a feature of preconditioning. A role for preconditioning is also supported by the demonstration that the time course of the warm-up phenomenon is consistent with that of classic ischemic preconditioning (lasting no longer than 60 and 90 minutes).[28] Indeed, we found that in patients with stable angina undergoing three consecutive exercise tests, the warm-up phenomenon observed within minutes of a first exercise test is a result of adaptation to ischemia, whereas warm-up phenomenon observed 2 hours after the second exercise test is a result of a training effect caused by peripheral mechanisms.[28] However, studies that have examined the cellular mechanisms of the warm-up phenomenon do not fully support this hypothesis. For example, the involvement of K_{ATP} channels in the warm-up phenomenon is uncertain. In fact, K_{ATP} channel blockade by glibenclamide, given in the attempt to prevent the warm-up phenomenon at a dose previously shown to block adaptation to ischemia during coronary angioplasty,[29] have yielded conflicting results.[30-33] Furthermore, adenosine receptors, which have been identified as key mediators in experimental ischemic preconditioning, do not seem to play a major role in the setting of the warm-up phenomenon. Indeed, both aminophylline, a nonselective antagonist of adenosine receptors, and bamiphylline, a selective antagonist of A_1 adenosine receptors, fail to prevent the warm-up phenomenon.[34,35] Thus, future work is necessary in order to better understand the mechanisms of the warm-up phenomenon, including studies on transmural distribution of myocardial perfusion and on triggers of ischemic preconditioning different from adenosine.

Coronary Angioplasty

Since its introduction in 1976, coronary angioplasty has provided a useful model for studying the effects of transmural myocardial ischemia due to controlled coronary occlusions in patients with coronary artery disease. Studies during coronary angioplasty have greatly contributed to the understanding of several pathophysiologic aspects of myocardial ischemia in humans, including the role of collateral circulation, stenosis severity, and small vessel function.[36-39] More recently, the experimental demonstration of preconditioning, together with the common clinical observation of fewer electrocardiographic ischemic changes and less anginal pain during sequential coronary balloon occlusion, led to the utilization of coronary angioplasty as a model for the study of ischemic preconditioning in humans. The procedure usually involves repeated intracoronary balloon inflations with intervening periods of reperfusion; the first period of ischemia may enhance the myocardial tolerance to subsequent balloon inflations via classic ischemic preconditioning. The first formal study aimed at assessing adaptation to ischemia during coronary angioplasty was published by Deutsch and coworkers[40] and involved 12 patients with an isolated obstructive stenosis in the left anterior descending coronary artery undergoing two sequential 90-second balloon inflations. In comparison with the initial balloon occlusion, the second occlusion was characterized by less subjective anginal pain, less ST-segment shift and lower mean pulmonary artery pressure, despite a reduction in cardiac vein flow and unchanged coronary wedge pressure. These findings have been observed in several other angioplasty studies,[29,41-44] confirming an adaptive response of the myocardium to repeated ischemic episodes, akin to ischemic preconditioning. Of note, some angioplasty studies failed to show adaptation to ischemia during repeated coronary occlusions, probably because they neglected some crucial methodologic aspects, such as short balloon inflations of less than 90 seconds, preinflation ischemia, or inadequate end points.[20,45]

A limitation of the angioplasty model of ischemic preconditioning is that the myocardial adaptation to ischemia observed following repeated coronary balloon occlusions is at least partially related to collateral recruitment.[46-48] However, although collateral recruitment during a first coronary balloon inflation does occur, further recruitment during following inflations is infrequent (in about 30% of the patients) and occurs only after multiple inflations.[20,45] Furthermore, it is still controversial whether ST-segment changes are a reliable indicator of a protected state[49-51]; yet, several studies in patients undergoing coronary angioplasty have shown that the ST-segment shift correlates with metabolic (i.e., lactate production), mechanical (i.e., regional wall motion abnormalities), and clinical (i.e., anginal pain) parameters of myocardial ischemia.[20,45]

The most convincing evidence that the adaptation to ischemia during repeated balloon inflations is mediated by ischemic preconditioning, however, comes from the observation that in this setting the adaptation to ischemia can be prevented or mimicked by agents that specifically prevent or mimic preconditioning in experimental models. Indeed, adaptation to ischemia during repeated coronary occlusions is prevented by glibenclamide,[29] adenosine antagonists,[41,42] phentolamine,[44] naloxone,[52] and caffeine,[53] whereas it is mimicked by adenosine,[43] enalaprilat,[54] morphine sulfate[55] bradykinin,[56] and nitroglycerin.[57,58]

Cardiac Surgery

Intermittent ischemia achieved by aortic cross-clamping in a fibrillating heart during coronary artery bypass grafting has been utilized as a clinical model of ischemic preconditioning. In this model the confounding effects due to collateral flow are overcome by utilizing global rather than regional ischemia. Yellon and coworkers[59] examined the effect of two ischemic episodes of 3 minutes, each followed by 2-minute reperfusion, on high energy phosphate metabolism during

TABLE 24–1 Studies on Nicorandil in Acute Coronary Syndromes

Clinical Setting	Reperfusion Treatment	Agent	Potential Mechanism	Results	Reference
Unstable angina	—	IV Nicorandil	Preconditioning	↓ Ischemic episodes and arrhythmias	Patel et al.[75]
Unstable angina	PTCA	IV Nicorandil	Preconditioning	↓ Levels of cardiac troponin T and I	Kim et al.[76]
AMI	Thrombolysis or PTCA	IC Nicorandil	↓ Reperfusion injury	↑ LV function	Sakata et al.[78]
AMI	Thrombolysis	Oral Nicorandil	↓ Reperfusion injury	↓ Arrhythmias	Sen et al.[79]
AMI	PTCA	IV Nicorandil	↓ Reperfusion injury	↑ LV function and in-hospital outcome	Ito et al.[80]
AMI	PTCA	IV Nicorandil	↓ Reperfusion injury	↓ Incidence of cardiovascular death or re-H for CHF	Ishii et al.[82]
AMI	PTCA	IV Nicorandil	↓ Reperfusion injury	No difference in LV size and LV ejection fraction compared to placebo	Kitakaze et al.[83]

HF, heart failure; IC, intracoronary; LV, left ventricular; PTCA, percutaneous transluminal coronary angioplasty; re-H: re-hospitalization.

10-minute cross-clamping, while the first distal coronary anastomosis was performed. Myocardial biopsies taken after the 10-minute ischemic insult exhibited a significantly higher ATP content than that found in controls not previously exposed to brief ischemic episodes, thus proving that the human myocardium shows the typical biochemical features of preconditioning observed by Murry and colleagues[1] in their classic canine model of ischemic preconditioning. Yet, Perrault and colleagues[60] have also reported that 3-minute aortic cross-clamping followed by 2-minute reperfusion before warm-blood cardioplegic arrest during coronary artery bypass surgery fails to provide any beneficial effect. Nevertheless, evidence that preconditioning may offer patients protection against irreversible myocyte injury comes from another study by Yellon and coworkers,[61] who showed a reduction of troponin T release in patients exposed to two periods of myocardial ischemia of 3 minutes each at the beginning of the revascularization operation. Furthermore, it has been shown that, in the setting of coronary artery bypass surgery, adenosine,[62-64] acadesine,[65] and bradykinin[66] are effective in improving postoperative left ventricular function. Finally, other studies have shown that volatile anesthetics, including enflurane and isoflurane, are able to optimize myocardial protection during cardiac surgery, probably through activation of K_{ATP} channels.[67-71]

ADENOSINE TRIPHOSPHATE–SENSITIVE POTASSIUM CHANNEL OPENERS AND ADENOSINE IN ACUTE CORONARY SYNDROMES

A tantalizing clinical application of pharmacologic preconditioning is in patients with acute coronary syndromes, in the attempt to slow down the progression of myocardial necrosis, thus increasing the time available for effective reperfusion. The exploitation of preconditioning, however, depends on the possibility of administering preconditioning drugs before ischemia, making this approach difficult in patients at low risk of MI, such as those with chronic stable angina. Conversely, it is well known that patients with unstable angina or with a recent MI have a higher risk of MI in the few months following the initial ischemic episode.[72] In this group of patients, the administration of drugs mimicking ischemic preconditioning in the time period at increased risk might slow necrosis rate in those patients who would eventually develop an acute myocardial infarction (AMI), thus increasing the time available for reperfusion therapy. The myocardium of patients with unstable angina, however, might already be preconditioned by prior ischemic episodes, limiting the potential advantages of preconditioning drugs. Another theoretical problem may be the development of tachyphylaxis to preconditioning agents. Indeed, Tsuchida and coworkers[73] have shown in a rabbit model that continuous infusion of a selective A_1 adenosine receptor agonist led to downregulation of the signaling mechanism and loss of protection. However, more encouraging data have been obtained recently using a different dosing schedule, in which the same drug was administered to rabbits by intermittent dosing over a 10-day period with persistence of myocardial protection assessed 48 hours after the last dose.[74]

Very few studies have evaluated the protective role of pharmacologic preconditioning strategies in patients with acute coronary syndromes (Tables 24-1 and 24-2). In particular, the preconditioning-mimetic drugs investigated so far are adenosine, acadesine (an adenosine-regulatory agent), and the only clinically available K_{ATP} channel opener licensed for cardiovascular use, nicorandil. Of note, adenosine was the first endogenous ligand to be identified as a trigger of the

TABLE 24–2 Studies on Adenosine in Acute Coronary Syndromes

Clinical Setting	Reperfusion Treatment	Agent	Potential Mechanism	Results	Reference
AMI	PTCA	IV Adenosine	↓ Reperfusion injury	↓ Infarct size	Garratt et al.[85]
AMI	Thrombolysis	IV Adenosine	↓ Reperfusion injury	↓ Infarct size (anterior infarction)	Mahaffey et al.[86]
AMI	PTCA	IC Adenosine	↓ Reperfusion injury	↑ LV function and in-hospital outcome	Marzilli et al.[88]
AMI	Thrombolysis or PTCA	IV Adenosine	↓ Reperfusion injury	No difference compared with placebo in the primary endpoint (new HF, re-H for HF, or death)	Ross et al.[89]
AMI	PTCA	AMP579	↓ Reperfusion injury	↓ Infarct size (anterior infarction)	Kopecky et al.[91]

HF, heart failure; IC, intracoronary; LV, left ventricular; PTCA, percutaneous transluminal coronary angioplasty; re-H: re-hospitalization. AMP579 is an adenosine receptor agonist.

cardioprotective action of experimental ischemic preconditioning and the mitochondrial K_{ATP} channel is thought to be the distal target or effector of protection.

Nicorandil

The first clinical trial aimed at assessing the cardioprotective role of nicorandil in patients with unstable angina was published by Patel and coworkers (CESAR 2 investigation).[75] This study suggests that opening of K_{ATP} channel with nicorandil, in addition to standard maximal anti-anginal therapy, results in a significant reduction in the incidence of myocardial ischemic episodes and tachyarrhythmias.[75] Of note, because the majority of patients were already on treatment with either oral or intravenous nitrates, it is unlikely that the beneficial effects of oral nicorandil were due to its vasodilatory properties. It is therefore possible that the protection observed in the nicorandil group was due to pharmacologic preconditioning resulting in a significant reduction in the number of ischemic events.[75] Recently, Kim and colleagues[76] randomized 200 patients with unstable angina to intravenous isosorbide dinitrate or intravenous nicorandil. A coronary angioplasty was performed 12 to 48 hours after infusion of each agent in 96 patients. Nicorandil was associated with a significant decrease in levels of cardiac troponin T and I at 6, 12, and 24 hours after angioplasty compared with isosorbide dinitrate.[76]

Further large scale randomized trials are warranted to assess the effects of nicorandil on prognosis and adverse outcome in this setting.

As pointed out earlier, the exploitation of ischemic preconditioning depends on the possibility of administering preconditioning drugs before the prolonged, potentially lethal ischemic insult (e.g., patients with unstable angina). However, some authors have proposed that the cardioprotective effects of preconditioning might also be operative during the reperfusion phase of ischemia-reperfusion injury resulting in a reduction in cytosolic calcium oscillations and free radical formation.[77] These observations prompted investigation into the potential cardioprotective properties of nicorandil following AMI. Sakata and coworkers[78] investigated the effects of an intracoronary bolus of nicorandil following successful coronary thrombolysis or primary angioplasty. They found that, compared with controls, nicorandil-treated patients exhibited improved restoration of myocardial blood flow to the infarcted myocardium as assessed by contrast echocardiography and improved regional wall motion at 1 month. Similar findings have been obtained by Sen and coworkers,[79] who evaluated the safety and efficacy of oral nicorandil as an adjunct to routine therapeutic management in patients with AMI. They showed that nicorandil was safe and well tolerated in the setting of AMI with no increase in adverse events compared with controls. They also showed a trend toward a reduction in development of Q-waves in patients presenting with subendocardial infarction and a reduced incidence of arrhythmias in the nicorandil-treated group. Ito and colleagues[80] investigated the effects of intravenous infusion of nicorandil in patients with AMI undergoing primary coronary angioplasty. They found that intravenous nicorandil in conjunction with coronary angioplasty is associated with better functional and in-hospital clinical outcomes compared with angioplasty alone. It is worth noting, however, that in the setting of AMI, the cardioprotective effects of nicorandil are probably related to an improvement in microvascular perfusion rather than to myocardial preconditioning, as suggested by the lesser frequency of no-reflow phenomenon in nicorandil-treated patients than in controls.[78,80]

Recently, Ishii and colleagues[81] demonstrated that nicorandil before coronary angioplasty exerts pharmacologic cardioprotective effects similar to ischemic preconditioning seen in patients with prodromal angina pectoris. The authors compared cardioprotective effects of intravenous nicorandil with preconditioning effects by prodromal angina in patients with AMI. In total, 368 patients with first AMI who underwent coronary angioplasty were randomly assigned to receive nicorandil 12 mg or a placebo intravenously just before coronary angioplasty. Subjects were assigned to 1 of 4 groups: 52 patients with prodromal angina were given placebo, 129 patients without prodromal angina were given nicorandil, 56 patients with prodromal angina were given nicorandil, and 131 patients without prodromal angina were given placebo. Coronary microvascular impairment after coronary angioplasty was prevented at similar frequencies in groups with prodromal angina and groups on nicorandil. Five-year rates for freedom from major cardiac events were significantly lower in the group without prodromal angina given placebo compared with the other three groups.[81] At 5 years, the addition of intravenous nicorandil to primary coronary angioplasty led to less incidence of cardiovascular death or rehospitalization for congestive heart failure, as well as various aspects of epicardial flow and microvascular function compared with placebo.[82]

The recently published single-blind, prospective, J-WIND trial randomized 276 AMI patients to receive intravenous nicorandil (0.067 mg/kg as a bolus, followed by 1.67 μg/kg per min as a 24-hour continuous infusion), and 269 the same dose of placebo.[83] At a median follow-up of 2.7 years, intravenous nicorandil did not affect the size of the left ventricular ejection fraction, although oral administration of nicorandil during follow-up increased the left ventricular ejection fraction between the chronic and acute phases.[83]

Thus, all these studies provide evidence for safety and tolerability of nicorandil in the setting of AMI; furthermore, they suggest that either intravenous or oral administration of this drug as an adjunct to standard reperfusion strategies improves microvascular perfusion of the ischemic myocardium and, therefore, possibly improves left ventricular function.

Adenosine

Adenosine or acadesine, an adenosine-regulating agent, have been shown to confer cardioprotection in the settings of coronary angioplasty and cardiac surgery,[20] but no clinical trial in patients with unstable angina has yet been reported. Thus, a potential therapeutic exploitation of preconditioning with adenosine or its analogues in the setting of unstable angina remains to be investigated.

Of note, adenosine, in addition to its role in myocardial ischemic preconditioning, has been shown to attenuate ischemia-reperfusion injury in animals, through inhibition of neutrophil activation, inhibition of oxygen free radical formation, and improvement of microvascular function, resulting in a reduction of infarct size and an improvement of left ventricular function and coronary blood flow.[84] This has prompted investigation into the potential cardioprotective properties of adenosine in patients with AMI. Garratt and coworkers[85] investigated the effects of intravenous adenosine and lidocaine in patients with AMI undergoing primary angioplasty. They found that moderate doses of adenosine may be given intravenously in this setting without unacceptable risk of complication and that, compared with historical controls, adenosine-treated patients had smaller infarcts at 6-week follow-up. These findings have been confirmed by a relatively larger multicenter, randomized trial (AMISTAD) designed to test the hypothesis that intravenous adenosine as an adjunct to thrombolysis would reduce myocardial infarct size.[86] Patients with anterior AMI assigned to adenosine had a 67% relative reduction in final infarct size as assessed by single photon emission computed tomography (SPECT)

imaging 6 days after the infarct; however, there was no reduction in the final infarct size observed in patients with non-anterior infarction, nor evidence of morbidity/mortality in-hospital benefit.[86] Experimental studies, however, have shown that the beneficial effect of adenosine on infarct size is remarkable and consistent when this agent is given before coronary occlusion, and that it is still present, but weaker, when adenosine is given before reperfusion, and negligible and inconsistent when adenosine is given during reperfusion.[84,87] Thus, the lack of an obvious beneficial impact of adenosine on clinical outcome observed in the AMISTAD trial[86] may be at least partially due to delayed adenosine administration (after thrombolytic administration) in about 50% of the patients. This drawback has been overcome in a recent small randomized trial in patients with AMI undergoing primary angioplasty, in which intracoronary adenosine was given right before balloon dilation.[88] In this study, in fact, intracoronary adenosine administration prevented the no-reflow phenomenon, improved ventricular function, and was associated with a more favorable clinical course.[88]

The AMISTAD-II[89] trial evaluated the effect of 3-hour intravenous infusion of either adenosine 50 or 70 μg/kg/minute or placebo on clinical outcomes in 2118 patients with evolving anterior AMI receiving thrombolysis or primary angioplasty. The primary end point was new congestive heart failure beginning more than 24 hours after randomization, or the first re-hospitalization for heart failure, or death from any cause within 6 months. Infarct size was measured in a subset of 243 patients by technetium-99m sestamibi tomography.[89] There was no difference in the primary end point between placebo and either the pooled adenosine dose groups or, separately, the 50-μg/kg/min and 70-μg/kg/min dose groups. Notably, the pooled adenosine group trended toward a smaller median infarct size compared with the placebo group. A dose-response relationship with final median infarct size was seen: 11% at the high dose and 23% at the low dose, a finding that correlated with fewer adverse clinical events.[89] Notably, in a post hoc analysis, adenosine infusion administered as an adjunct to reperfusion therapy within the first 3.17 hours onset of evolving anterior AMI enhanced early and late survival, and reduced the composite clinical end point of death or heart failure at 6 months.[90] Since the major limitation of this study was that the sample size was too small to confirm that the observed adenosine-related reduction in the combined clinical end point was statistically significant, a more robustly powered investigation of this relatively safe and inexpensive drug as adjunctive therapy to reperfusion is warranted to demonstrate whether the reduced infarct size achieved with the higher infusion dose translates into enhanced event-free survival.

In the randomized, placebo-controlled ADMIRE trial, the administration of an adenosine agonist with high affinity for A_1 and A_2 receptors, that is, AMP579, given intravenously before primary angioplasty was associated with a trend toward smaller infarct size and greater myocardial salvage in patients with anterior MI.[91]

Recently, data from the Multicenter Study of Perioperative Ischemia (McSPI) Research Group from the IREF trial have been reported.[92] This study randomized 2698 patients undergoing coronary artery bypass grafting (CABG) surgery to receive placebo or acadesine by intravenous infusion (0.1 mg/kg/min; 7 hours) and in cardioplegia solution (placebo or acadesine; 5 μg/mL) in order to assess the safety and efficacy of acadesine for reducing long-term mortality among patients with postreperfusion MI. Acadesine treatment reduced mortality by 4.3-fold, from 27.8% to 6.5% (P = .006), with the principal benefit occurring over the first 30 days after MI. The acadesine benefit was similar among diverse subsets, and multivariable analysis confirmed these findings.[92] This study successfully moves forward the concept of preconditioning as a therapy from bench to bedside. Nevertheless, large clinical trials are needed to confirm the cardioprotective effects of adenosine (or its agonists) in the setting of acute coronary syndromes.

EMERGING STRATEGIES FOR CARDIOPROTECTION

Remote Ischemic Preconditioning

A more amenable and less invasive approach to cardioprotection might be achieved by remote ischemic preconditioning, whereby brief ischemia in one region or organ protects distant tissue or organs from a sustained episode of ischemia. Przyklenk and colleagues[93] showed that a brief circumflex artery occlusion could reduce the myocardial infarct size induced by the subsequent sustained occlusion of the left anterior descending artery. This notion was further evaluated in subsequent studies which suggested that brief ischemia of noncardiac tissue such as the kidney,[94] the intestine,[95] or skeletal muscle[96] could also protect the myocardium against a subsequent MI. Remote ischemic preconditioning may also modify myocardial gene expression by upregulation of cytoprotective genes and suppression of proinflammatory genes that are potentially involved in the pathogenesis of ischemia-reperfusion injury.[97] Furthermore, it has been used to attenuate myocardial injury in a porcine model of coronary artery bypass graft surgery[98] and in children undergoing corrective cardiac surgery for congenital heart disease.[99] Recently, Hausenloy and colleagues conducted a single-blinded randomized controlled study in 57 adult patients undergoing elective CABG surgery assigned to either a remote ischemic preconditioning group or to a control group after induction of anaesthesia.[100] Remote ischemic preconditioning consisted of three 5-minute cycles of right upper limb ischemia, induced by an automated cuff-inflator placed on the upper arm and inflated to 200 mm Hg, with an intervening 5 minutes of reperfusion during which the cuff was deflated, before arrival in the catheterization laboratory for percutaneous coronary intervention. Remote ischemic preconditioning significantly reduced overall serum troponin T release at 6, 12, 24, and 48 hours after surgery.[100] More recently, a randomized control study in 242 patients undergoing elective percutaneous coronary intervention (PCI) demonstrated that remote ischemic preconditioning reduced median troponin I release at 24 hours after the procedure, chest pain and ST-segment deviation during the procedure, and major adverse cardiac and cerebral event rate at 6 months (Fig. 24-2).[101] Protection was time dependent, with the greatest benefit observed in those with shorter cuff-to-balloon times.[101] This large randomized study suggested that remote ischemic preconditioning, a simple, safe, noninvasive and cheap procedure, has the potential to affect the prognosis of patients with stable coronary disease treated with coronary stent implantation.

Ali and colleagues randomized 82 patients to abdominal aortic aneurysm repair with remote ischemic preconditioning or conventional abdominal aortic aneurysm repair (control) and evaluated the incidence of myocardial and renal injury.[102] Two cycles of intermittent cross-clamping of the common iliac artery with 10 minutes ischemia followed by 10 minutes reperfusion served as the remote ischemic preconditioning stimulus. Remote ischemic preconditioning reduced the incidence of myocardial injury (in terms of cardiac troponin I release) by 27% and renal impairment (evaluated by serum creatinine levels) by 23%, independently from other covariables.[102]

These data strongly indicate that remote preconditioning may confer myocardial protection, thus justifying the need for large clinical trials investigating the use of remote

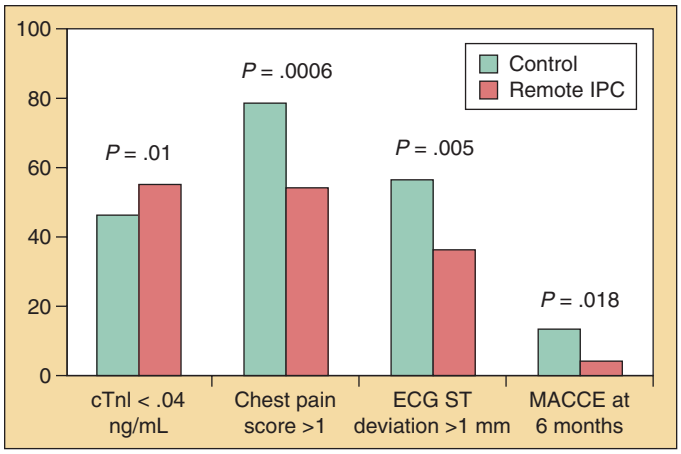

FIGURE 24–2 Incidence of plasma cTnI <0.04 ng/mL, chest discomfort, ECG ST-segment deviation, and major adverse cardiac and cerebral events (MACCE) at 6 months after elective percutaneous coronary intervention among patients randomized to receive remote ischemic preconditioning (IPC, $n = 104$) or control ($n = 98$). *(From Hoole SP, Heck PM, Sharples L, et al: Cardiac remote preconditioning in coronary stenting (CRISP Stent) study. A prospective, randomized, control trial. Circulation 2009;110:820-827.)*

preconditioning in other situations in which myocardial ischemia is expected, such as adult and pediatric cardiac surgery.[103]

Postconditioning

Although prompt coronary reperfusion is a keystone for the treatment of AMI, acutely restoring blood flow to the myocardium carries the potential to exacerbate injury from that present at the end of ischemia. Reperfusion injury potentially offsets the optimal salvage of myocardium achieved during cardiac surgery, PCI, or cardiac transplantation.

Early strategies to attenuate reperfusion injury applied concepts derived from cardiac surgery, in which protecting the myocardium from ischemia-reperfusion injury was a mainstay of the operative strategy.[104] Surgical cardioprotective strategies were centered on modifying the conditions of reperfusion (cardiopulmonary bypass, reperfusate pressure, pulsatility, temperature) or the composition of the reperfusate (pH, osmolality, substrates such as glucose, amino acids, and adjunct drugs) in order to reduce infarct size after a fixed period of ischemia.[105]

A critical early observation was that reperfusion damage could be modified by slowly and progressively initiating reflow (termed *postconditioning*).[106,107] This postconditioning theory arose from the simple application of preconditioning, suggested by Zhi-Qing Zhao more than a decade ago, by moving the preconditioning "stimulus" to the beginning of reperfusion, and thereby ostensibly modifying reperfusion.

Initial experiments in which several cycles of 5 minutes' reperfusion and 5 minutes' coronary occlusion preceded complete reperfusion failed to reduce infarct size. The experiments were terminated and the concept was filed in storage for nearly 10 years. Research on reperfusion injury matured during this interval and it was found that many reactions proceeded rapidly after the onset of reperfusion. They are as follows: (1) Oxidants were generated within minutes of reperfusion[108]; (2) neutrophils were activated and adhered to coronary vascular endothelium; (3) damage to the coronary vascular endothelium worsened as reperfusion continued[109]; and (4) calcium dyshomeostasis caused rapid damage to cell structures.[110] The rapid nature of these triggers of reperfusion resurrected the concept of postconditioning and led to the compression of the postconditioning algorithm from several minutes of each occlusion-reperfusion cycle to seconds (30 seconds in dogs to 10 seconds in rats and mice). Experimental studies demonstrated that this progressive and intermittent reperfusion may reduce infarct size, restore postischemic contractile function, decrease edema in the area at risk, and avoid blood flow defects characterized as a *no-reflow* response.[106,111] Postconditioning attenuates multiple triggers of reperfusion injury including oxidants, proinflammatory cytokines, neutrophils, and proapoptotic regulators, and reduces damage not only to cardiomyocytes, reducing infarct size and apoptosis, but also to coronary vascular endothelium.

Postconditioning has been shown to be effective in all species tested, with the possible exception of pigs.[107] Its application in patients presenting for PCI during AMI had been suggested in implications to several experimental publications, but questions were immediately raised regarding potential injury to the target coronary artery from repeated balloon inflations, possible dislodgement of atheromatous material, or dissection of the coronary artery.

Recently, Staat and coworkers[112] tested the concept of postconditioning in humans. Thirty patients, submitted to coronary angioplasty for ongoing AMI were enrolled in this prospective, randomized, multicenter study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control subjects underwent no further intervention, whereas postconditioning was performed within 1 minute of reflow by four episodes of 1-minute inflation and 1-minute deflation of the angioplasty balloon. Creatine kinase release was significantly reduced in the postconditioning compared with the control group, with a 36% reduction in infarct size. Also myocardial blush grade, a marker of myocardial reperfusion, was significantly increased in postconditioned compared with control subjects.[112] Notably, the postconditioned group exhibited a significant 7% increase in left ventricular ejection fraction compared with control at 1 year.[113] This study first suggested that postconditioning by coronary angioplasty protects the human heart during AMI and supported the notion that reperfusion damage is a clinical entity rather than a laboratory curiosity.

Recent studies provided mechanistic insights in cardioprotection showing that it is now possible to protect the reperfused myocardium by activating prosurvival kinase signaling pathways (reperfusion injury salvage kinase pathway).[114] Both pre- and postconditioning activate the same key pathways, which include phosphatidylinositol 3-kinase-Akt and extracellular signal-regulated kinase.[114,115] Upstream may be activation of G-protein coupled receptors, and the many downstream events include key phosphorylations of endothelial nitric oxide synthase and inhibition of the apoptosis promoters.[114,115] Pharmacologic agents such as glucagon-like peptide 1, erythropoietin, atorvastatin, and atrial natriuretic peptide,[116] all of which reduce infarct size by activating these enzymatic pathways, are being examined in proof-of-concept studies in patients with AMI who are undergoing coronary angioplasty.

As in the case of ischemic preconditioning, protective pathways activated by postconditioning appear to converge on the mitochondria, in particular through the inhibition of mitochondrial permeability transition pore opening.[117] Moreover, the protective effect of postconditioning may directly or additionally be related to beneficial anti-inflammatory or antioxidant effects, decreased extracellular levels of noxious metabolites such as protons and lactate, or delayed washout of adenosine, a well-established mediator of preconditioning.[118] Along these lines, a recent study[119] demonstrated for the first time in humans that remote postconditioning[120,121] and preconditioning share mechanistic similarities, with pro-

tection being dependent on K_{ATP} channel activation, in preventing endothelial ischemia-reperfusion injury.

Large clinical trials will be required to ensure that these new cardioprotective strategies improve clinical outcomes in patients with AMI. Such new cardioprotective strategies may also benefit patients who sustain acute myocardial ischemia-reperfusion injury during coronary-artery bypass grafting or cardiac transplantation surgery and patients surviving a cardiac arrest.

CONCLUSIONS

Several lines of evidence indicate that adaptation of the myocardium to ischemia observed during in vitro studies on human atrial trabeculae and in different clinical settings is mainly due to ischemic preconditioning and is, at least partially, mediated by the stimulation of adenosine receptors and by the opening of K_{ATP} channels. These findings suggest that in patients at high risk of MI (i.e., patients with unstable angina or recent MI, drugs known to elicit this endogenous form of protection might have a relevant therapeutic role. In this regard, a first clinical trial conducted in patients with unstable angina shows that nicorandil, in addition to standard maximal anti-anginal therapy, results in a significant reduction in the incidence of myocardial ischemic episodes and tachyarrhythmias.[75] However, no other large clinical trial aimed at assessing the cardioprotective role of preconditioning mimetic agents in patients with unstable angina are available to date. In addition to preconditioning-mimetic agents such as adenosine and nicorandil, another promising therapeutic approach to cardioprotection in patients with unstable angina may be the utilization of sodium/hydrogen exchange inhibitors (e.g., cariporide and eniporide), recently proved to be cardioprotective in experimental studies[122-124] and in the clinical setting of acute coronary syndromes and cardiac surgery.[125-128] The mechanisms by which sodium/hydrogen exchange inhibitors work, involve a decrease in the influx of sodium into ischemic cells. This ultimately inhibits the exchange of sodium for calcium. Calcium overload of the myocardial cell is thought to lead to major disruption of metabolism and architectural disruption, including the formation of contraction band-type necrosis and precipitation of calcium phosphate granules within the mitochondria.

In patients with AMI, new strategies for cardioprotection (i.e., postconditioning) and pharmacologic agents given after the onset of coronary ischemia may be useful adjuncts to reperfusion treatment if they reduce reperfusion injury.[129] In this regard, both K_{ATP} channel openers and adenosine have been shown to be cardioprotective (probably independently of their preconditioning-mimetic effects) particularly when given right before reperfusion, thus making this approach mainly feasible in the setting of primary coronary angioplasty.[80,81,88,89]

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CHAPTER 25

Inflammation and Immunity as Targets for Drug Therapy in Acute Coronary Syndrome

E. Marc Jolicoeur and Christopher B. Granger

Inflammation has been associated with myocardial infarction, even before the recognition that acute coronary thrombi cause coronary occlusion and a time-dependent loss of myocardial muscle.[1] In response to injury, the immune system plays a crucial role in clearing the necrotic cells and the matrix debris, which initiates the process of scar formation. Both the immune and the inflammatory systems act in concert to coordinate the migration of inflammatory cells into the injured myocardium. Inflammation is essential to heal the infarction. It has been hypothesized that expansion of the infarction is a common maladaptive process, as is the case of reperfusion injury. Preclinical and clinical research on reperfusion injury has been a major focus over the past two decades. Controversy exists, however, as to whether and when reperfusion injury plays an important role in clinical myocardial infarction, and the modulation of the inflammatory response in the hours following an acute coronary syndromes has not resulted in demonstrable clinical benefits. Animal models of reperfusion injury show that the spontaneous reperfusion of recently infarcted myocardium triggers several intense inflammatory signals that culminate in excessive cell death and adverse myocardial remodeling. Inflammation is a major component of reperfusion injury and several adjunctive anti-inflammatory strategies have been tested in clinical trials. This chapter will focus on clinical investigation targeting the inflammatory and the immune system in patients with recent myocardial infarction.

THE ADVERSE CONTRIBUTION OF INFLAMMATION DURING THE REPERFUSION INJURY

Although aggressive revascularization and optimal medical therapy have resulted in improved outcome, mortality and morbidity remain high following acute myocardial infarction (AMI). In a contemporary cohort of patients with AMI, the in-hospital mortality ranged from 7% in the contemporary international Global Registry of Acute Coronary Events (GRACE)[2] up to 28% in the MONICA Project.[3] To date, the only intervention proven to reduce infarct size is early revascularization, either through fibrinolytic therapy or primary percutaneous coronary intervention (PCI). Although restoration of blood flow to the infarcting myocardium is essential to prevent irreversible injury, reperfusion itself may worsen tissue injury in excess of what would be produced by ischemia alone. The observation in randomized clinical trials of fibrinolytic therapy versus control of excess mortality the first day following fibrinolytic therapy may reflect this phenomenon. This second wave of damages, called the reperfusion injury, has been thought to paradoxically aggravate the initial damages caused by ischemia.

If reperfusion injury is occurring in human myocardial infarction, the total benefit of a reperfusion (the myocardial salvage) can be expressed as the diminution of the necrotic zone due to timely reperfusion minus the paradoxical damage caused by reestablishment of flow to the injured myocardium (the reperfusion injury). The reperfusion injury, in return, can be broken down into two major components: vascular reperfusion injury and cellular reperfusion injury. Vascular reperfusion injury results in the "no reflow" seen when the infarct-related epicardial artery is reopened but coronary flow to the downstream myocardium is not re-established. The vascular injury is assumed to be caused by capillary plugs made of polymorphonuclear leukocytes (PMNs) and inflammatory microthrombi with distal embolization. Cellular reperfusion injury is a complex phenomenon that involves several defective pathways, among which the acute inflammatory response plays an important role. This cell injury results from the release of reactive oxygen radicals, intracellular calcium overload, the opening of the mitochondrial permeability transition pores, and apoptosis. The acute inflammatory response has also been divided into distinct components: the activation of the complement cascade, the intramyocardial infiltration by PMN leukocytes, and the toll-like receptor mediated pathways. The principal components of the reperfusion injury are summarized in Table 25-1.

TABLE 25–1	The Components of the Reperfusion Injury
Total myocardial salvage =	**[Diminution of necrotic core] − [reperfusion injury]**
Reperfusion injury =	[Vascular reperfusion injury] + [cellular reperfusion injury] + [apoptosis]
Vascular reperfusion injury =	[Inflammatory cells capillary plugging] + [inflammatory microthrombi] + [distal embolization]
Cellular reperfusion injury =	[Reactive oxygen radicals] + [intracellular calcium overload] + [opening of the mitochondrial permeability transition pores] + [acute inflammatory response]
Acute inflammatory response =	[Complement system activation] + [toll-like receptor-mediated pathways] [polymorphonuclear leukocyte infiltration]

There are several comprehensive reviews on the mechanisms of reperfusion injury[4] and on interventions targeting the potential mediators of cellular or "lethal" reperfusion injury.[5,6] Likewise, strategies used to reduce the inflammation in the coronary vasculature can be reviewed in the chapter on plaque passivation (see Chapter 26). This chapter will focus on drugs and interventions that specifically target the inflammation and immunity processes occurring in the myocardium after an acute coronary syndrome. A detailed understanding of the role played by the inflammatory and immune systems is required before exploring the overall disappointing clinical experience seen with many cardioprotective strategies intended to reduce reperfusion injury. If the phenomenon of reperfusion injury is clinically meaningful, then any intervention that can modulate the inflammatory response holds the potential to limit infarct size, to promote an improved infarct healing, and to reduce mortality.

The Immunoinflammatory Response to Ischemia and Reperfusion

When Reimer and Jennings initially described their wavefront hypothesis of AMI,[7] little was known about the role of neutrophils, the complement cascade, and toll-like receptor mediated pathways to myocardial damage after reperfusion. Of interest, the idea of myocardial protection following myocardial infarction emerged around the same time.[8] Since then, more than 10 distinct anti-inflammatory strategies have been tested in clinical trials to limit the adverse consequences of ischemia and reperfusion (Table 25-2). With the possible exception of corticosteroids, the strategies tested in the clinic have been based on the hypothesis that the early inflammatory reaction associated to the reperfusion on an infarcted myocardium is harmful, and therefore should be down-modulated.

The healing of the heart following a transmural infarct occurs in three overlapping phases: the inflammatory phase, the proliferative phase, and the maturation phase.[9] The inflammatory phase starts when the necrosed myocytes release ligands normally sequestered away from the immune

TABLE 25–2	Selected Randomized Clinical Trials Targeting Inflammatory and Immunity During Acute Coronary Syndrome				
Trial, Year (n)	**Agent, Dose, Study Design**	**Time of Drug to Symptoms Onset**	**Revascularization**	**1° End Point**	**Comments**
Nonsteroidal anti-inflammatory drugs (NSAIDs)					
TAMI-4 trial,[34] 1989 (*n* = 50) STEMI	Iloprost IV, 2 ng/kg/min × 48 hr Open label	—	Fibrinolysis	LVEF change at 7 days worst with iloprost	The combination of rt-PA plus iloprost at the doses employed did not improve either the early or the late follow-up coronary artery patency
NUT-2,[37] 2002 (*n* = 120) UA/NSTEMI	Meloxicam 15 mg IV once, then 15 mg PO daily × 30 day Open label	—	—	The composite of death, MI, and recurrent angina at 90 days significantly better with meloxicam	No adverse complications associated with meloxicam treatment were observed. Trial performed before the widespread adoption of early invasive PCI in NSTEMI
Corticosteroids					
SoluMedrol Sterile Powder AMI,[44] 1986 (*n* = 1118) STEMI	Methylprednisolone IV, 30 mg/kg q 3 hr × 2 vs. placebo Double-blind	Within 6 hr (group 1) or 6-12 hr (group 2)	—	Mortality at 28 days did not differ between groups	Methylprednisolone not associated with myocardial rupture or cardiac aneurysm
Statins					
ARMYDA-ACS,[50] 2007, (*n* = 171) NSTEMI	Atorvastatin PO, 80 mg vs. placebo Double-blind	7 days before PCI	PCI	The composite of death, MI, and unplanned revascularization reduced with atorvastatin	High-risk ACS patients were excluded from the study.
Adenosine and agonists					
AMISTAD,[67] 1999 (*n* = 236) STEMI	Adenoscan IV, 70 µg/kg/min × 3 hr vs. placebo Open label	Within 6 hr	Fibrinolysis	^{99m}Tc SPECT infarct size at 7 days 33% smaller with adenosine	The reduction of infarct size more pronounced in patients with anterior infarction. Patients randomized to adenosine tended to experience more adverse clinical events

TABLE 25–2 Selected Randomized Clinical Trials Targeting Inflammatory and Immunity During Acute Coronary Syndrome—Cont'd

Trial, Year (n)	Agent, Dose, Study Design	Time of Drug to Symptoms Onset	Revascularization	1° End Point	Comments
Marzilli et al,[204] 2000 (*n* = 54) STEMI	Adenosine IC, 4 mg over 1 min vs. placebo Single blind	Within 3 hr	Primary PCI	No-reflow less frequent with adenosine. The composite of death, MI, and CHF better with adenosine	The IC injection of adenosine was safe and well tolerated. No bradyarrhythmias were observed. The rates of TIMI 3 flow at the end of the PCI were significantly better in adenosine
ATTACC,[69] 2003 (*n* = 608) STEMI	Adenosine item IV 10 μg/kg/min × 6 hr vs. placebo Double-blind	Within 6 hr	Fibrinolysis	Echocardiogram LVEF at hospital discharge did not differ between groups	Recruitment stopped due to apparent lack of efficacy after interim analysis. Cardiovascular mortality of 8.9% with adenosine and 12.1% with placebo at 1 yr (P = .2)
ADMIRE,[75] 2003 (*n* = 311) STEMI	Adenosine agonist AmP579 IV 15 vs. 30 vs. 45 μg/kg vs. placebo × 6 hr Double-blind	Within 6 hr	Primary PCI	^{99m}Tc SPECT infarct size at 5-9 days did not differ between groups	
AMISTAD II,[68] 2005 (*n* = 2118) STEMI	Adenosine IV 50 vs. 70 μg/kg/min × 3 hr vs. placebo Double-blind	Within 6 hr	Fibrinolysis 58.3% Primary PCI 40.2%	The survival free of death, CHF, and rehospitalization at 6 mo did not differ between groups	Patients treated with the adenosine 70 μg/kg/min had a smaller infarct size compared with placebo (11% vs. 27% of the left ventricle, P = .02)
P-selectin inhibitors					
RHAPSODY,[86] 2003, (*n* = 598) STEMI	rPSGL-Ig IV, 5 mg vs. 25 mg vs. 75 mg vs. placebo Double-blind	Within 6 hr	Fibrinolysis	Time to ST-segment resolution proportional to the rPSGL-Ig doses	Neither ^{99m}Tc SPECT infarct size at 7 days nor the LVEF at 30 days differed between groups
PSALM,[84] 2006 (*n* = 88) STEMI	rPSGL-Ig IV, 75 vs. 150 mg vs. placebo Open label	Within 6 hr	Fibrinolysis	$^{13}NH_3$ myocardial blood flow and ^{18}FDG metabolic activity did not differ at 30 days between the groups	Trial prematurely stopped after lack of efficacy shown in accompanying larger trial. No difference seen for ST-segment resolution and LVEF improvement
CD11/CD18 integrin receptor blockade					
LIMIT AMI,[87] 2001 (*n* = 394) STEMI	rhuMAb CD18 IV, bolus 0.5 vs. 2.0 mg/kg vs. placebo Double-blind	Within 12 hr	Fibrinolysis	Corrected TIMI frame count, or the rate of TIMI 3 flow at 90 min did not differ between groups	There was neither treatment effect on the infarct size nor on the rate of ECG ST-segment resolution. There was a trend toward more bacterial infections with rhuMab CD18
FESTIVAL,[205] 2001 (*n* = 60) STEMI	Hu23F2G IV, 0.3 vs. 1.0 mg/kg vs. placebo Double-blind	Within 6 hr	Primary PCI	^{99m}Tc SPECT infarct size at 5-9 days did not differ between groups	One patient found to have antibodies against Hu23F2G. No significant differences in adverse events (including infections) noted between the groups
HALT AMI,[182] 2002 (*n* = 420) STEMI	Hu23F2G IV, 0.3 or 1.0 mg/kg vs. placebo Double-blind	Within 6 hr	Primary PCI	^{99m}Tc SPECT infarct size at 5-9 days did not differ between groups	No difference in the infarct size was seen in the subgroup of patients with anterior MI or those presenting within 2 hr of symptoms onset. Clinical events at 30 days very low
Complement inhibitors					
COMMA,[106] 2003 (*n* = 960) STEMI	C5 inhibitor Pexelizumab IV, bolus alone vs. bolus + infusion vs. placebo. B: 2 mg/kg, I: 0.05 mg/kg × 20 hr Double-blind	Within 6 hr	Primary PCI	72-hr CK-MB AUC did not differ between groups	The mortality at 90 days significantly lower with pexelizumab bolus + infusion compared with placebo (1.8% vs. 5.9%, P = .014)
COMPLY,[105] 2003 (*n* = 943) STEMI	C5 inhibitor pexelizumab, same as COMMA Double-blind	Within 6 hr	Fibrinolysis	72-hr CK-MB AUC did not differ between groups	Adjunctive pexelizumab was given 10 min after lytics on average. No significant effect on clinical outcomes
APEX-AMI,[98] 2007 (*n* = 5745) STEMI	C5 inhibitor pexelizumab vs. placebo, B: 2 mg/kg, I: 0.05 mg/kg x 20 hr Double-blind	Within 6 hr	Primary PCI	Mortality at 30 days did not differ between groups	The trial was intended to enroll 8500 patients initially. The composite end points of death, shock, or heart failure did not differ between groups

TABLE 25–2 Selected Randomized Clinical Trials Targeting Inflammatory and Immunity During Acute Coronary Syndrome—Cont'd

Trial, Year (n)	Agent, Dose, Study Design	Time of Drug to Symptoms Onset	Revascularization	1° End Point	Comments
Thielmann,[104] 2006 (*n* = 57) STEMI	C1-esterase inhibitor Berinert vs. placebo, B: 40 UI/kg IV, I: 20 UI/kg × 6 hr, Open label	Within 24 hr of symptoms onset	Emergency CABG surgery	24-hr TnI AUC did not differ between groups	Patients treated with C1-INH within 6 hr of symptom onset had significantly lower peak maximum TnI level
ITF-1697					
PARI MI,[110] 2004 (*n* = 402) STEMI	ITF-1697 IV, dose finding, bolus, followed by infusion (0.1, 0.5, 1.0, or 2.0 μg/kg/min) vs. placebo × 24 hr Double-blind	Within 12 hr	Primary PCI	The HBDH AUC infarct size and clinical outcome at 30 days did not differ between groups	ITF-1697 did not affect the post-PCI perfusion assessed by corrected TIMI flow, blush grade, or ST-segment resolution
Erythropoietin					
Lipsic et al,[129] 2006 (*n* = 22) STEMI	Darbepoetin-α IV, 300 μg Open-label	Within 6 hr	Primary PCI	Peak CK and CK-MB did not differ between groups, but were numerically higher in the darbepoetin group	No adverse events were recorded during the 30-day follow-up. At 4 months, the LVEF were similar between groups (52% ± 3% for EPO vs. 48% ± 5% for placebo)
Liem et al,[127] 2007 (*n* = 51) NSTEMI	Epoetin-α IV, 40,000 IU vs. placebo Open label	Within 8 hr of first positive troponin I	—	72-hr CK-MB AUC did not differ between groups	The rates of reinfarction were similar at 1 yr. The authors described a blood pressure augmentation in the hours following the administration of erythropoietin
Binbrek et al,[131] (*n* = 236) STEMI	β-Epoetin IV, 30,000 IU vs. standard therapy Open label	Within 6 hr	Tenecteplase	CK-MB gram equivalents (infarct size) did not differ between groups	The LVEF measured by echocardiogram before discharge was similar between the groups
FX06					
F.I.R.E.,[157] 2009 (*n* = 234) STEMI	FX06 400 mg IV vs. placebo Double-blind	Within 6 hr	Primary PCI	Late gadolinium-enhanced CMR infarct size at 5 days did not differ between groups	At 5 days, FX06 was associated to a significant reduction in the necrotic core zone measured with CMR. At 40 days, this difference was no longer significant
Cyclosporine and analogues					
Piot et al,[162] 2008 (*n* = 58) STEMI	Cyclosporine IV, 2.5 mg/kg vs. placebo Single blind	Within 12 hr	Primary PCI	72-hr CK AUC was significantly better in patients treated with cyclosporine, whereas the Tn I AUC was not	In a substudy of 27 patients, MI size measured by MRI was 20% smaller in cyclosporine-treated patients

B, bolus; C1-INH, complement-1 inhibitors; CK, creatinine kinase; CMR, cardiac magnetic resonance; I, infusion; IC, intracoronary; IV, intravenous; ECG, electrocardiogram; FDG, fludeoxyglucose (18F); HBDH, α-hydroxybutyrate dehydrogenase; MRI, magnetic resonance imaging; PO, per os (by mouth), rt-PA; recombinant tissue-plasminogen activator, rhuMAb; recombinant human monoclonal antibody; rPSGL-Ig; recombinant P-selectin glycoprotein ligand-immunoglobulin; TnI, troponin I; UA, unstable angina.

system inside the cells. Intracellular ligands, such as heat shock proteins or the fibronectin fragments, are perceived as a threat by the immune system, which activates several immunoinflammatory pathways, such as the toll-like receptor (TLR)-mediated pathways,[10] the nuclear factor NF-κB,[11] and the complement cascade. Of all the immune system compartments involved in the overall healing process, only a few have been shown to contribute specifically to reperfusion injury.

PMNs are a first-line defense against foreign antigens and play a key role in the acute inflammatory response following tissue injury. After a persistent coronary artery occlusion, PMNs accumulate in the myocardium, reaching a peak within 24 hours and then diminishing over the course of 1 week.[1] In experimental models of ischemia and reperfusion, the PMN accumulation is accelerated compared with what is observed in the non-reperfused infarct.[12] In dogs, for instance, the neutrophil count is 80% higher in the reperfused hearts compared with non-reperfused hearts.[12] Neutrophils accumulate in the reperfused myocardium and may cause further infarction through their cytotoxic armamentarium (Fig. 25-1).[13,14] When activated by appropriate stimuli, neutrophils undergo a respiratory burst that leads to the genesis of superoxide and oxygen radicals, which are major mediators of lethal cellular injury.[15,16] In addition to their direct toxic effect, oxygen radicals induce vasoconstriction and aggravate the post-ischemic coronary endothelial dysfunction. Likewise, the neutrophil-produced oxidants can depress the calcium transport in myocytes and sarcoplasmic reticulum and exacerbate ventricular dysfunction.[17] The degranulation of activated PMNs exposes the interstitium to several proteolytic enzymes that can directly cause myocyte damage. For instance, collagenases and elastases cleave the interstitial matrix molecules into chemotactic peptide fragments, which may subsequently recruit monocytes into the necrotic myocardium. The recruitment of monocytes and

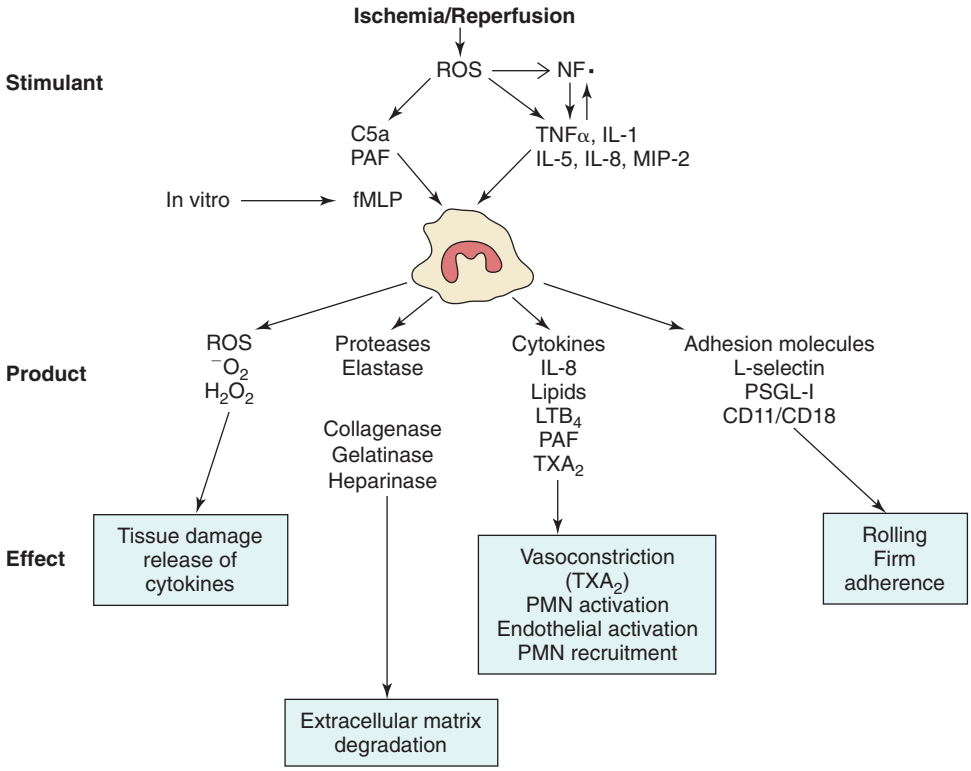

FIGURE 25–1 The activation of neutrophils. Schematic diagram of activation of neutrophils, and neutrophil-derived products that participate in lethal myocardial ischemia-reperfusion injury. Reactive oxygen species generated by neutrophils or coronary vascular endothelial cells stimulate the immediate release of proinflammatory factors in ischemic-reperfused myocardium, as well as increased transcription of factors through NF-nB. These factors then activate neutrophils to generate reactive oxygen species, proteases, various cytokines and lipid mediators, and upregulate surface expression of adhesion molecules that interact with endothelium and cardiomyocytes. CD, cluster determinant; H_2O_2, hydrogen peroxide; Isch, ischemia; LTB_4, leukotriene B_4; MIP-2, macrophage inflammatory protein-2; n-fMLP, N-formyl peptides; $-O_2$, superoxide anions; -OH, hydroxyl anion; Rep, reperfusion; ROS, reactive oxygen species; XA_2, thromboxane A_2. *(Reproduced with permission from Vinten-Johansen J: Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury. Cardiovasc Res 2004;61:481-497.)*

other inflammatory cells is also maintained by the release of proinflammatory arachidonic acid metabolites that amplify and perpetuate the inflammatory reaction. In addition to their cytotoxic effect, neutrophils block the microcirculation to contribute to the reflow phenomenon. PMNs are larger and less compliant than red blood cells. Once activated, PMNs become less easily deformable and tend to adhere in clusters to the endothelial cells to form microcirculatory plugs.[18] Finally, the protease and free oxygen radicals released by neutrophils can directly activate the complement cascade,[19-21] that further accentuates the inflammatory reaction and the cellular damage.

The complement system is part of the innate immune system and has a fundamental protective role against infective agents. The complement system can be activated by the classic, the alternative, and the lectin pathways, which all converge at the cleavage of C3 into C3a + C5a, two potent anaphylatoxins capable of recruiting inflammatory cells, and into C3b which flags cells for phagocytosis (Fig. 25-2). Once activated, the complement system amplifies the inflammatory reaction and perpetuates an environment favorable to fight foreign invaders. In the terminal portion of the complement cascade, C5 cleavage initiates the formation of the C5b-9 membrane attack complex (MAC), which is a transmembrane channel that causes direct tissue injury through osmotic lysis. While desirable when the organism has to fight a microbiologic invader, the non-specific complement-induced amplification of the inflammatory response may be harmful to the host in the specific context of ischemia-reperfusion injury.

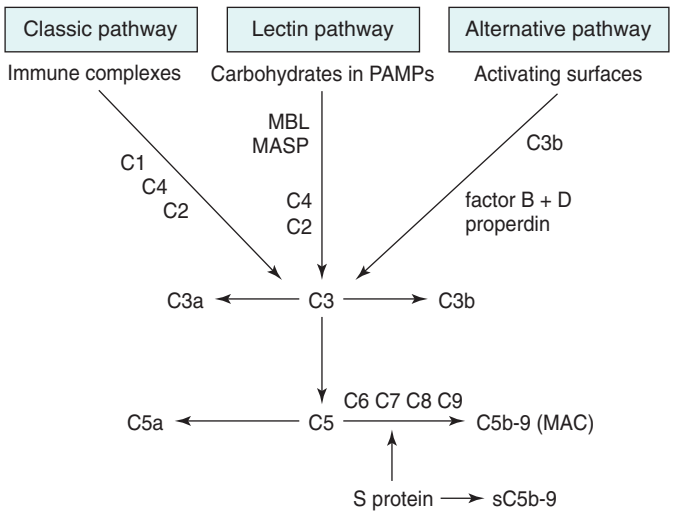

FIGURE 25–2 The activation of the complement system. All three activation pathways merge at the cleavage of C3 and lead to the generation of anaphylatoxins (C3a, C5a) for the recruitment of inflammatory cells, flagging of cells for phagocytosis (C3b) and the generation of the membrane attack complex (MAC: C5b-9) for cell lysis. Regulation of the complement system is extremely important and each step is controlled by several inhibitors. MASP, mannose-binding lectin-associated serine protease; MBL, mannose-binding-lectin; PAMPs, pathogen-associated molecular pattern. *(Reproduced with permission from Haahr-Pedersen S, Bjerre M, Flyvbjerg A, et al: Level of complement activity predicts cardiac dysfunction after acute myocardial infarction treated with primary percutaneous coronary intervention. J Invasive Cardiol 2009;21:13-19.)*

The accumulation of complement in the ischemic heart soon after reperfusion suggests its involvement in reperfusion injury.[22] In vivo, the inhibition of the complement cascade during myocardial infarction has been shown to result in decreased levels of proinflammatory complement byproducts (sC5b-9),[23,24] in reduced chemotaxis of polymorphonuclear leukocytes in the myocardium, and in a reduction of myocyte necrosis[24] and apoptosis.[24]

Clinical Investigations with Anti-Inflammatory and Immunosuppressive Agents

Aspirin and the Nonsteroidal Anti-inflammatory Drugs

The interaction between platelets and the inflammatory system are numerous. It is therefore no surprise that interventions aimed at inhibiting platelet function may exert, in parallel, significant anti-inflammatory effects. Aspirin has a compelling mortality benefit during AMI.[25] In addition to its antiplatelet properties, aspirin exerts some anti-inflammatory effects that may contribute to some of the mortality benefit observed after myocardial infarction.[26,27] In animal models, aspirin triggers the synthesis of lipoxins (known as the aspirin-triggered LXA4) that vigorously inhibits leukocyte chemotaxis during ischemia and reperfusion injury.[28] Nonsteroidal anti-inflammatory drugs (NSAIDs), on the other hand, have been extensively studied because of their possible deleterious effect on the endothelium and on atherosclerotic plaques.[29] In dogs, ibuprofen has been shown to reduce both the infarct size and leukocyte accumulation inside the infarcted tissue.[30] This is in the context, however, of the well-established effect of indomethacin on impairing infarct healing and leading to aneurysm formation.[31]

In a retrospective study meant to assess the effect of NSAIDs in the pre-aspirin era, Sajadieh and colleagues looked at the pre-randomization use of NSAIDs among the Danish Verapamil Infarction Trial (DAVIT) II trial.[32] The authors hypothesized that NSAIDs other than aspirin may also improve the prognosis after AMI. After correction for age, sex and hypertension, the use of NSAIDs before myocardial infarction was associated with a non-significant reduction in mortality (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.28 to 1.25; $P = .17$), and major cardiac events (HR, 0.67; 95% CI, 0.37 to 1.19; $P = .17$). While this is useful for hypothesis generation, the association may well be due to confounding.

Prostacyclin (PGI_2) is a member of the eicosanoid family that naturally prevents the formation of clot by inhibiting platelet activity and by causing arterial vasodilatation. In experimental settings, prostacyclin was shown to facilitate fibrinolysis and reduce myocardial stunning following infarction.[33] These early experiments served as the bases for the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-4 trial which tested iloprost, a synthetic analogue of prostacyclin, in combination to rt-PA in 50 patients with evolving ST-segment elevation myocardial infarction (STEMI).[34] Compared with rt-PA alone, the combination of intravenous iloprost (2 ng/kg/min for 48 hr) and rt-PA neither affected the rates of infarct-related vessel patency at 90 minutes (44% vs. 66% respectively, $P = .26$) nor improved the ejection fraction recovery at 7 days (+2.9% vs. –2.3% respectively, $P = .05$).

The inhibitors of cyclooxygenase-2 (COX-2) have been linked to increased cardiovascular risk when administered for chronic conditions.[35] Paradoxically, a selective COX-2 inhibition has been shown to reduce the macrophage infiltration and to preserve the ventricular function after myocardial infarction in rodents.[36] At least one trial has suggested a protective effect of short-term administration of COX-2 inhibitor to patients with acute coronary syndrome. In the Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2 (NUT-2) pilot study, patients with non–ST-segment elevation myocardial infarction (NSTEMI) randomized to 30 days of meloxicam (a selective COX-2 inhibitor) experienced less recurrent angina, myocardial infarction, or death than the patients randomized to placebo (21.7% vs. 48.3% respectively, $P = .004$, $n = 120$) at 90 days after initial hospitalization.[37] In this small study, the benefits were mainly driven by the high rates of recurrent angina in the placebo-treated patients. Neither the investigators nor the patients were blinded to the treatment assignment. These findings await validation in a large double-blind trial.

Corticosteroids

Corticosteroids have a pleiotropic effect on the immune system. They were among the first immunomodulators studied in AMI.[38] Corticosteroids exert adverse effects on the cardiovascular system, such as dyslipidemia and hypertension.[39] Since the 1970s, several case series have linked the use of corticosteroids with left ventricular free wall rupture in the days following AMI.[39-41] The mechanism by which corticosteroids prevent healing of myocardial infarction is not entirely known; it may relate to impaired scar formation of the degenerative process responsible for the peripheral myopathy seen in patients treated with chronic corticosteroids.[39] The steroid-dependent attenuation of the sympathetic innervations of the infarct region could also contribute to impaired healing.[42] On the other hand, the powerful immunosuppressive effect of corticosteroids may modulate the inflammatory response that could have beneficial effects in the short term.

Corticosteroids have been tested in patients with acute coronary syndrome.[43] In the Muna randomized trial, methylprednisone was compared with placebo in patients with recent-onset unstable angina. While 48 hours of methylprednisone decreased C-reactive protein levels compared with placebo, it had no apparent effect on subsequent coronary events. In fact, a trend toward a better event-free survival was seen in the placebo-control group. The trial was underpowered to address the effect of steroids on clinical events. In 1986, the Solu-Medrol Sterile Powder AMI Studies Group reported the results of a double-blind, placebo controlled trial that tested whether a single dose of methylprednisolone (30 mg/kg IV) reduced 28-day mortality in 1118 patients with recent myocardial infarction complicated by cardiac failure.[44] Per design, the trial hypothesized that an effect of methylprednisolone could depend on time since symptom onset. When administered within 6 hours of symptoms onset, methylprednisolone did not seem to affect mortality compared with placebo (11.7% vs. 9.9%, P = NS). However, when started more than 6 hours after the onset of symptoms, Solu-Medrol significantly reduced mortality at 48 hours (10.4% vs. 14.7%, $P = .04$) and at 6 months ($P = .03$). Interestingly, similar rates of cardiac aneurysms (1.2% vs. 0.5%, $P = .45$), and cardiac ruptures (1.7% vs. 2.5%, $P = .47$) were observed between methylprednisolone and placebo-treated patients.

In a recent meta-analysis of 11 controlled trials including 2646 patients, a 26% relative mortality reduction was observed with the use of corticosteroids within the first few hours following AMI (odds ratio [OR], 0.74; 95% CI, 0.59 to 0.94; $P = .02$).[45] In a sensitivity analysis which excluded the non-randomized study, the previously observed mortality benefit with steroids was no longer present (OR, 0.95; 95% CI, 0.72 to 1.26). Importantly, no clear association was observed between myocardial rupture and corticosteroids, calling into question the conventional wisdom that steroids impair infarct healing. While none of the trials was performed in the modern era of thrombolytics and aggressive percutaneous revascularization, the available evidence suggests no

evidence of either substantial benefit or harm from corticosteroids in AMI.

Statins

Just like aspirin, long-term statin administration improves the prognosis of patients across the entire spectrum of acute coronary syndromes (ACS).[46-48] However, the short-term benefits of statin therapy early after ACS are equivocal. In a recent meta-analysis, the initiation of a statin within 14 days following the onset of an acute coronary event did not reduce death, myocardial infarction (MI), or stroke at 4 months.[49] Fewer studies have assessed the protective role of statins when present before the occurrence of an ACS. In this regard, the Atorvastatin for Reduction of Myocardial Damages during Angioplasty (ARMYDA)-trial has provided interesting insights on the mechanism of action of statins. In ARMYDA, a pretreatment with 80 mg of atorvastatin at least 12 hours before the percutaneous coronary intervention (PCI) resulted in a significant reduction of the composite incidence of death, myocardial infarction, and unplanned revascularization at 30 days (5% vs. 17% for placebo, $P = .01$), mainly through a reduction in peri-procedural infarctions.[50] Atorvastatin resulted in a lower average percent increase of C-reactive protein level after the PCI (63% ± 114% vs. 147% ± 274% for placebo). After adjusting for key clinical predictors (NSTEMI, left ventricular ejection fraction [LVEF] below 40%, the use of glycoprotein IIb/IIIa inhibitors and beta blockers), atorvastatin remained a significant predictor of favorable clinical outcome. In a substudy of ARMYDA, the levels of soluble intercellular cell adhesion molecule-1 (ICAM-1) and E-selectin were significantly less increased at 24 hours following the PCI in patients treated with atorvastatin, suggesting a modulatory effect of statin on leukocytes and endothelial cell interactions.[51]

The acute benefit seen with statins in ACS patients cannot be solely explained by the cholesterol-lowering effect, which requires a longer duration of treatment. This so-called *pleiotropic effect* of statins could be in part due to a favorable modulation of the inflammatory system.[52,53] Animal experiments have suggested that statins can reduce the infarct size, related to a decrease in endothelial expression of P-selectin on endothelial cells and CD18 on leukocytes, leading to a reduced neutrophil extravasation into the reperfused myocardium.[54,55] Together with the stabilization of the endothelial function and the microcirculatory vasodilatation, the immunomodulatory effects of statins appear to favor survival of cardiomyocytes following ischemia/reperfusion.[56]

Adenosine and Its Agonists

Adenosine is an endogenous purine nucleoside that antagonizes several of the metabolic, biochemical and inflammatory pathways that may be involved in reperfusion injury (Fig. 25-3). Adenosine and its receptor appear to be important elements of the intrinsic protective mechanism of the myocardium against ischemic insult.[57] When subjected to hypoxia, myocardial and endothelial cells naturally release adenosine which, in turn, brings myocardial cells into a phenotype of sustained tolerance against ischemia.[58] This phenomenon, called preconditioning, is incompletely understood but involves the inhibition of oxygen free radical formation,[59] the repletion of cardiomyocytes and endothelial cells with high-phosphate stores,[60] and the increase in nitric oxide bioavailability.[61] Equally important is the cardioprotective effect of adenosine through the modulation of inflammation. Adenosine has a marked inhibitory effect on neutrophils by limiting their reactive oxygen species generation[62] and their adherence to endothelial cells, possibly via a down-modulation of CD11/CD18 expression.[63] In addition to its antineutrophil effects, adenosine may also serve as a metabolic switch that senses tissue injury and acts to reduce the production of inflammatory cytokines,[58] such as tumor necrosis factor-α, interleukin-12, or macrophage inflammatory protein (MIP)-1a.[64] In animal models of reperfusion injury, adenosine has consistently improved coronary blood flow, reduced infarct size, and improved left ventricular functional recovery.[6]

The cardioprotective effect of adenosine and its agonists has been assessed in distinct clinical scenarios, including acute coronary syndromes, high-risk PCI,[65] and coronary artery bypass graft (CABG) surgery.[66] The Acute Myocardial Infarction Study of ADenosine (AMISTAD)-I[67] and AMISTAD-I[68] trials assessed the role of adenosine in myocardial infarction. The 236-patient AMISTAD-I trial showed a 33% reduction ($P = .03$) in infarct size measured by single-photon-emission computed tomography (SPECT) ^{99m}Tc sestamibi with adenosine compared with placebo. In the subgroup of patients with anterior wall infarction, the difference was even more important, with a 67% relative reduction in final infarct size (15% vs. 45.5% of left ventricle respectively, $P = .01$). While the number of adverse clinical events was low, there was a numerical excess of death (10 vs. 6) and congestive heart failure (13 vs. 8) among patients treated with adenosine. These findings prompted the AMISTAD-II trial, a phase III randomized, double-blind trial designed to compare progressive doses of adenosine to placebo in 2118 patients with anterior STEMI. In this setting, adjunctive adenosine was no better than placebo at prolonging event-free survival (death, in-hospital congestive heart failure [CHF] and rehospitalization for CHF) at 6 months (84% vs. 82%, $P = .43$). Interestingly, in a substudy, patients treated with adenosine tended to have smaller median infarct size compared with patients treated with placebo (17% vs. 27% of the left ventricle, $P = .07$). Moreover, patients treated with the highest dose of adenosine (70 μg/kg/min) had the smallest infarct size, suggesting a dose-response relationship (11% of the left ventricle, $P = .02$ vs. placebo). As noted by the investigators, there was a significant association between the infarct size and the occurrence of CHF or death. The discrepancy between the actual effect of adenosine on infarct size and the clinical outcomes remains unexplained, but may relate to the relatively low power of this moderately sized trial. It also, however, calls into question the validity of surrogate outcomes—such as infarct size—to assess the clinical effects of investigational new drugs.

The benefits suggested by the AMISTAD trials were not confirmed by the ATTenuation by Adenosine of Cardiac Complications (ATTACC) trial.[69] In ATTACC, 608 patients with STEMI were randomized to either adjunctive low-dose adenosine (10 μg/kg/min) or placebo, administered with fibrinolysis. The relatively small dose of adenosine was chosen after concerning rates of adverse events were observed with higher doses (40 μg/kg/min). In this context, the LVEF was similar between the adenosine and the placebo-treated patients (44% vs. 45% respectively, P = NS), along with the wall motion score index (1.53 vs. 1.50, respectively, P = NS). Based on this apparent lack of benefit, recruitment in the trial was stopped after less than two thirds of the patients originally planned had been enrolled. At 12 months, the cardiovascular mortality was 8.9% with adenosine and 12.1% with placebo (OR, 0.71; 95% CI, 0.4 to 1.2; $P = .2$). As was the case with AMISTAD-I, the effect size appeared to be more impressive in the subgroup of patients with anterior STEMI (OR, 0.53; 95% CI; 0.23 to 1.24; $P = .09$). Because of the early termination of recruitment, the results should be interpreted with caution.[70]

In parallel to the AMISTAD and ATTACC trials, a series of trials have assessed the use of adjunctive adenosine agonist during AMI. The adenosine agonist AMP579 has mixed affinities for the adenosine A1 and A2 receptors. The A1 receptor is of major importance in mediating the anti-ischemic action of adenosine.[71] The A2 receptor, on the other hand, has a

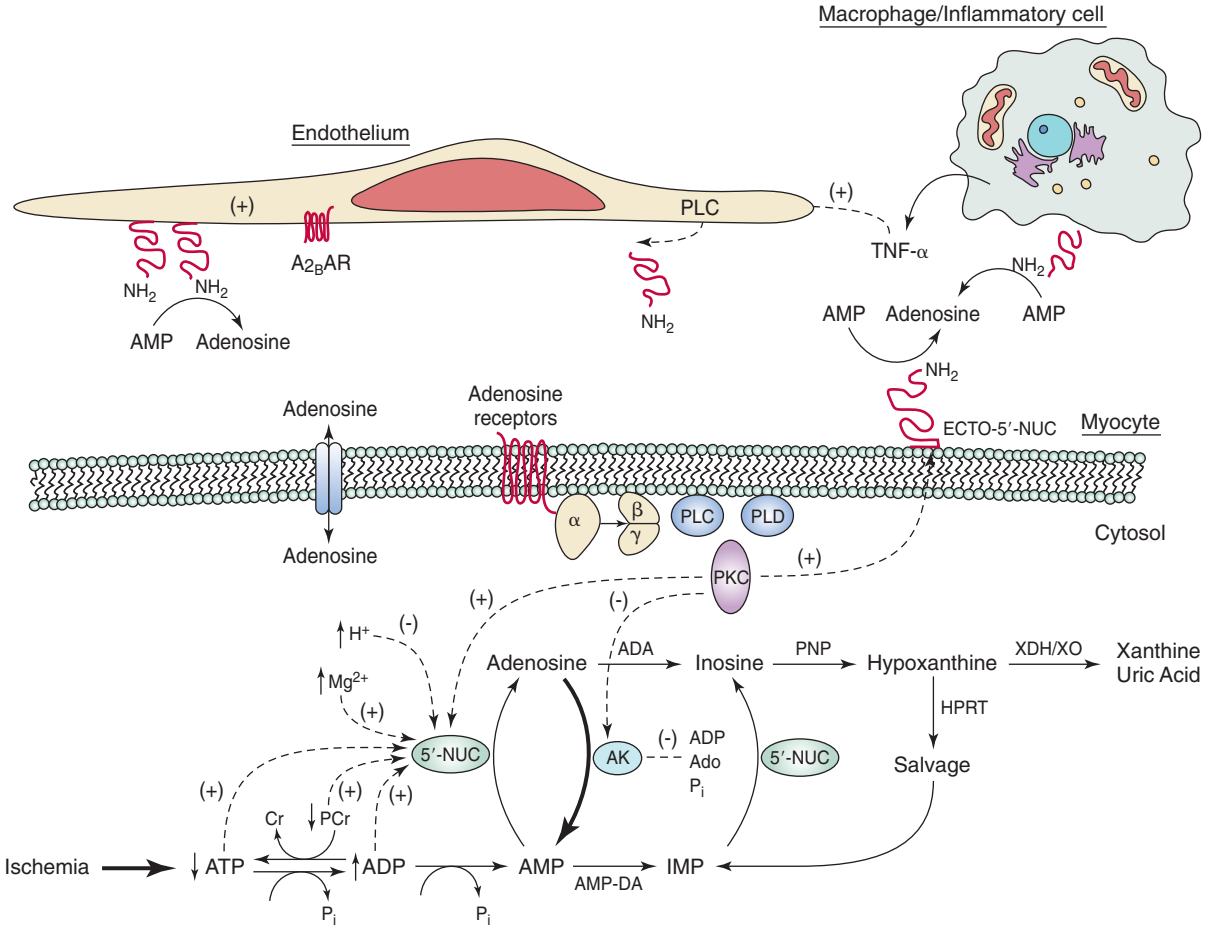

FIGURE 25–3 Anti-inflammatory pathways impacted by adenosine. A summary of pathways of adenosine formation and catabolism in the heart and their potential modulation during ischemia-reperfusion. Broken arrows reflect regulatory processes, with plus (+) and minus (–) symbols denoting activation or inhibition of pathways during de-energization/ischemia, respectively. Whereas catabolism of adenosine to inosine, hypoxanthine, xanthine, and uric acid is shown within the myocytes, deamination also occurs extracellularly, and these reactions occur with high activity in vascular cells. AK, adenosine kinase; AMP-DA, AMP deaminase; Cr, creatine; ECTO-5′-NUC, ecto-5′-nucleotidase; HPRT, hypoxanthine phosphoribosyl transferase; 5′-NUC, 5′-nucleotidase; PCr, phosphocreatine; P_i, inorganic phosphate; PKC, protein kinase C; PLC, phospholipase C; PLD, phospholipase D; PNP, purine nucleoside phosphorylase; TNF-α, tumor necrosis factor-α; XDH/XO, xanthine dehydrogenase/xanthine oxidase. *(Reproduced with permission from Headrick JP, Hack B, Ashton KJ: Acute adenosinergic cardioprotection in ischemic-reperfused hearts. Am J Physiol Heart Circ Physiol 2003;285:H1797-H1818.)*

more controversial contribution but appears to reduce the neutrophil adherence[72] and the subsequent damages during reperfusion injury.[73] In animal models of myocardial reperfusion injury, AMP579 has demonstrated superior cardioprotective effects compared with adenosine, possibly due to a superior inhibition of the vascular and myocardial tissue injury induced by neutrophils.[74] The AmP579 Delivery for Myocardial Infarction REduction (ADMIRE) trial was designed to find the most efficient dose of AmP579 in patients with STEMI treated with primary PCI.[75] To this end, 311 patients were randomized to either three different doses of AmP579 or placebo intravenously over 6 hours. No differences were seen in the final infarct size or the myocardial salvage index after adjustment for infarct-related artery, the time to reperfusion, and the initial TIMI flow. Likewise, the rates of adverse events were similar between the groups at 4 weeks and 6 months. ADMIRE did not demonstrate a benefit of AmP579 on infarct size or clinical outcomes.

Taken together, the trials presented in this section fail to show a clear clinical benefit of adjunctive adenosine with a timely reperfusion therapy. Additional studies are required, however, to fully explore the consequence of the beneficial effect of adenosine on infarct size and microvascular function.

Anti-Leukocyte Therapies

The endothelium serves as a natural barrier that protects the organ tissue from certain elements circulating in the blood. The endothelium is normally responsible to orchestrate the trafficking of leukocytes into the myocardium (see Fig. 25-3). In response to hypoxia, the endothelium undergoes a series of transcriptional and non-transcriptional changes similar to those seen during acute inflammation.[76] PMNs normally migrate into the ischemic tissue. Once in place, PMNs are thought to cause direct tissue damage and to amplify the inflammatory response during the reperfusion.[77] During an AMI, the microvascular damage and disruption of the endothelium barrier allow a massive influx of PMNs into the necrotic core and the surrounding viable myocardium. Likewise, PMNs secrete factors that disrupt the endothelial barrier and favor the formation of tissue edema.[78]

Leukocytes transmigrate tissue through a series of complex steps that involve anchoring molecules expressed by the endothelium. Circulating neutrophils expressing P-selectin glycoprotein ligand 1 (PSGL-1) are initially caught by the endothelial receptor P-selectin (CD62P). This low-affinity interaction allows the neutrophils to slow their course and roll on the endothelium until they adhere more firmly. This process is mediated by the ligation of the leukocyte β2

integrins CD11a/CD18 and the endothelial ICAM-1. Once tightly bound to the endothelium, the leukocytes can transmigrate into the ischemic tissue, where they release toxic reactive oxygen species and other proinflammatory substances.

After a myocardial infarction, the pharmacologic interventions targeting the leukocytes can be regrouped in three distinct targets: the inhibition of leukocyte adhesion molecule synthesis (such as CD11a/CD18), the inhibition of receptor engagement and endothelial cell adhesion (such as P-selectin), and the inhibition of inflammatory mediator release, such as platelet activation factor (PAF), and leukotriene B_4 (LTB_4). Both P-selectin and CD11a/CD18 have recently been tested in patients with STEMI.

P-Selectin Inhibitors

P-selectin (CD62P) is an adhesion molecule that plays a critical role in the migration of leukocytes through the vascular walls. The ligand of P-selectin, PSGL-1, is constitutively expressed by leukocytes. P-selectin is involved in the adhesion of platelets to the endothelium and has been shown to play an important role in the process of atherogenesis. Convincing studies have shown that animals lacking P-selectin have a decreased tendency to develop atherosclerotic plaques.[79] After promising animal experiments, the interference between P-selectin and PSGL-1 by the way of a monoclonal antibody was expected to facilitate the fibrinolysis and to decrease the infarct size by controlling the migration of leukocytes into the necrotic areas.[80-83] Because of its antithrombotic and anti-inflammatory effects, P-selectin inhibition appeared to be a promising target during acute MI.

The P-selectin Antagonist Limiting Myonecrosis (PSALM) trial tested a recombinant P-selectin glycoprotein ligand-immunoglobulin (rPSGL-Ig) in patients with STEMI presenting within 6 hours of symptom onset and treated with alteplase.[84] The engineered P-selectin antagonist combined the high-affinity ligand of the amino-terminal portion of PSGL-1 with an Fc (fragment crystallizable) region of the human IgG1. Patients were randomly assigned to a single intravenous bolus of either 75 mg of rPSGL-Ig, 150 mg of rPSGL-Ig, or placebo. The study tested the potential benefit of rPSGL-Ig on infarct size reduction using positron emission tomography to quantify the myocardial blood flow in the infarct territory, normalized for the systemic equilibrated blood pool. A total of 88 patients were enrolled before the trial was prematurely stopped by the sponsor. At 5 days, the normalized infarct size was not statistically different between the patients treated with placebo and the patients treated with either the low or the high doses of rPSGL-Ig (9.1% vs. 3.8% vs. 4.3%). The PSALM trial was stopped after a larger trial (RHAPSODY) failed to show any benefit of adjunctive rPSGL-Ig on the speed of ST-segment resolution and the reduction of infarct size in nearly 600 STEMI patients treated with fibrinolysis.[85,86] The RHAPSODY trial failed to show any significant effect of rPSGL-Ig on improvement of the LVEF, and the occurrence of death, stroke, and MI at 30 or 180 days. Unlike what was expected based on the animal data, there was a significant delay in myocardial reperfusion seen in patients treated with rPSGL-Ig, as shown by a significant prolongation of time to ST-segment resolution ($P = .008$). The redundancy of the inflammatory pathways in mammals may account for the lack of efficacy of a selective inhibition of P-selectin.[79]

CD11/CD18 Integrin Receptor Blockade

Neutrophils start to accumulate at the periphery of the necrotic myocardium as early as 8 hours after the start of the infarction.[13] Leukocytes transmigrate after they ligate their β_2 integrins CD11a/CD18 to ICAM-1. Using a rationale similar to with the P-selectin inhibitors, the blockade CD11/CD18 integrin receptor has been tested in two independent randomized controlled trials. The LIMIT-AMI trial was designed to define the safety and the efficacy of a rhuMAb CD18, a recombinant humanized monoclonal antibody against the CD18 subunit of the β_2 integrin adhesion receptors in 394 patients with AMI.[87] This randomized, double-blind trial compared two intravenous doses of the study drug (0.5 mg/kg vs. 2.0 mg/kg) to placebo, administered concomitantly with thrombolytic therapy. At 90 minutes after the start of fibrinolysis, the corrected TIMI frame count (primary end point) was similar between the groups, as was the percent of patients with a resolution of their ST-segment elevation resolution at 3 hours. The myocardial infarct size (assessed by ^{99m}Tc-sestamibi SPECT) was also similar, as were the rates of adverse clinical events. Compared to placebo, the systemic administration of the study drug resulted in a peak of circulating white blood cells at 24 hours, which rapidly resolved by 72 hours, with no apparent effect on other blood compartments.

The HALT-MI trial tested whether Hu23F2G, a humanized antibody directed against all the isoforms of the CD11/CD18 integrin receptors,[182] would reduce the infarct size in patients with AMI treated with primary PCI. The HALT-MI randomized 420 patients either to Hu23F2G (0.3 mg/kg or 1.0 mg/kg) or placebo given prior to primary PCI. The left ventricle infarct size measured by SPECT was used as the primary study end point. The study drug was administered as a single intravenous bolus over 1 to 2 minutes. The doses of Hu23F2G used in the trial were shown to saturate up to 80% of the CD11/CD18 integrin receptors for 12 to 24 hours in healthy volunteers. The final infarct size for the intention-to-treat population was similar in the 0.3 mg/kg, 1.0 mg/kg, and the placebo groups (16% vs. 17.2% vs. 16.4%, respectively; $P = .80$). Infarct sizes measured at baseline with the creatine kinase MB (CK-MB) area under the curve (AUC) for 24 hours were also similar. No difference in the rate of adverse clinical events at 30 days was detected. As was the case for the LIMIT-AMI trial, minor infections (mainly urinary tract infection) were more common in the active treatment groups. Together, the LIMIT-AMI and the HALT-MI trial show lack of beneficial cardiac effects of CD18 blockade in patients with AMI.

The time elapsed between the start of the myocardial infarction and the administration of the blockers of the CD11/CD18 integrin receptor varied significantly between animals and humans. This difference has been suggested as part of the explanation for the discrepant findings seen between the animal experiments and this (and other) clinical trials. In most animal experiments, the study drug was administered within 45 to 60 minutes after the ligation of the coronary artery. In the LIMIT-AMI study, the median time to symptom onset was 2.7 hours, for instance. The delays seen in humans may have resulted in a greater burden on endothelial cell barrier rupture. Assuming this were true, the greater endothelial permeability may in return have allowed a free circulation of neutrophils into the injured myocardium therefore bypassing the usual Mac-1 intercellular adhesion mechanism. Interestingly, no favorable effects were seen with the late administration of the CD11/CD18 integrin receptor blocker in experimental myocardial infarction.[89-96]

Complement Inhibitors

The complement inhibitors in general and pexelizumab in particular are amongst the most studied anti-inflammatory agents in ACS. The development program for pexelizumab enrolled more than 15,000 patients with an ischemic cardiac disease in diverse randomized investigations.[97] Pexelizumab is one of the few anti-inflammatory drugs formally tested in a phase III clinical trial of AMI.[98]

Two inhibitors of the complement system have been tested in patients with STEMI: the classical pathway, through the

inhibition of C1-(esterase); and the final common pathway, through the inhibition of C5. C1-(esterase) inhibitors have been shown to considerably reduce the reperfusion injury in translational models of AMI.[99,100] In 2002, de Zwaan and coworkers reported on the effect a C1-inhibitor purified from human plasma (Cetor; CLB, the Netherlands) and administered for 48 hours in patients with a recent AMI.[101] The study drug was started no sooner than 6 hours after the onset of symptoms. In this series, a dose-dependent reduction of complement activity was observed. In the subgroup of patients successfully reperfused with thrombolytics, the area under the curve for troponin and creatinine kinase-MB_{mass} was significantly reduced compared with untreated control patients (36% and 57%; $P = .001$). The intravenous administration of C1-(esterase) inhibitors, which prior to this experiment was limited to patients with hereditary angioedema, was deemed safe at doses up to 100 U/kg in adult patients with recent STEMI. The medication appears to have a narrow therapeutic window; extensive thrombosis was found in pigs receiving 200 U/kg of C1-inhibitor before coronary reperfusion.[102] Safety concerns about C1-(esterase) inhibitors have been raised after 9 deaths due to venous thrombosis were observed in neonates who received more than 300 U/kg of C1-inhibitor to reduce capillary leak during major cardiac surgery.[101,103]

More recently, another C1-(esterase) inhibitor was assessed in 57 patients with ongoing STEMI treated with reperfusion by emergency coronary artery bypass surgery.[104] Patients were randomized to either the inhibitor (ZLB Behrig, Marburg, Germany) or matching placebo. All surgeries were performed using standard cardioplegia techniques. In this context, the peak maximum troponin I serum levels were not significantly different between the groups, showing no benefit of C1-(esterase) inhibition in this small study. A subgroup analysis suggested that the treatment could reduce the infarct size if administered within 6 hours of symptom onset. Interestingly, the efficacy of C1 inhibition was confirmed by a significant increase in the serum C1-inhibition activity along with a reduced C3c and C4 complement fragment concentration at 24 hours in the blood of patients enrolled in the active treatment arm. No drug-related adverse events were reported. Of note, no postoperative coagulation or thrombotic disorders were observed. At 30 days, the rates of death, stroke, major bleeding, and renal failure were similar between the groups.

Pexelizumab is a recombinant humanized monoclonal antibody to C5. Pexelizumab blocks the amplification of the inflammatory reaction triggered by the complement cascade by inhibiting the conversion of C5 to C5a, an anaphylatoxin, and to C5b, a precursor of the C5b-9 membrane attack complex (MAC). The COMPlement inhibition in myocardial infarction treated with thromboLYtics (COMPLY) trial was a phase II investigation designed to assess the efficacy of pexelizumab as an adjunctive to fibrinolysis in patients with ongoing STEMI.[105] The trial randomized 943 patients to either a single pexelizumab bolus (2.0 mg/kg), or to a pexelizumab bolus plus an infusion (0.05 mg/kg/hr × 20 hr) or to matching placebo. The median infarct size, as determined by the CK-MB AUC, did not change by treatment nor did the 90-day composite incidence of death, CHF, cardiogenic shock, or stroke (bolus, 18.4%; bolus plus infusion, 19.7%; placebo, 18.6%).

In parallel to the COMPLY trial, the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial assessed whether pexelizumab decreased infarct size in STEMI patients reperfused by primary PCI.[106] To this end, 960 patients were randomized to either a single pexelizumab bolus (2.0 mg/kg), or a pexelizumab bolus (2.0 mg/kg) with an infusion (0.05 mg/kg/hr × 20 hr) or placebo. The bolus of pexelizumab or its matching placebo was to be given before the first device activation. While the administration of pexelizumab effectively inhibited the plasma complement activity, it did not reduce the infarct size, as measured by the CK-MB AUC ($P = .89$). Likewise, the 90-day composite of death, new or worsening heart failure, and stroke occurred in 8.5% of the bolus plus infusion patients versus 11.1% of the placebo patients (relative risk [RR], 0.77; 95% CI, 0.46 to 1.29). Of interest, pexelizumab given as a bolus plus an infusion was associated with a nominally significant reduction in mortality (RR, 0.30; 95% CI, 0.11 to 0.81), and in cardiogenic shock (RR, 0.55; 95% CI, 0.23 to 1.29), when compared to placebo. At 6 months, the difference in mortality was still significant (RR, 0.43; 95% CI, 0.20 to 0.94). The mortality among patients treated with a single bolus of pexelizumab was intermediate to the mortality observed with the bolus plus the infusion and the placebo groups, suggesting a dose-response relationship. The apparent contradiction between the improved survival and the lack of reduction in infarct size with pexelizumab in the COMMA trial led the investigators to hypothesize that the study drug may have mediated its effect through a reduction in inflammation at a systemic level, and/or through other effects on healing such as reduced apoptosis. In the COMMA trial, higher plasma levels of C-reactive protein and interleukin-6 (IL-6) levels at baseline, 24 hours, and 72 hours were significantly associated with increased mortality. Compared with placebo, patients treated with pexelizumab experienced a lowering of circulating levels of C-reactive protein and IL-6 at 24 hours after study drug administration (25.5 mg/L vs. 17.1 mg/L, $P = .03$, and 63.8 pg/mL vs. 51.0 pg/mL, $P = .04$, respectively).[107] This hypothesis and the suggestion of a mortality benefit found in COMMA were then tested for validation in a phase III trial, the APEX-AMI trial.

The Assessment of Pexelizumab in Acute Myocardial Infarction (APEX AMI) trial compared pexelizumab (bolus plus infusion) to placebo as adjunctive to primary PCI.[98] APEX-AMI was a multicenter, double-blind, placebo-controlled, phase III study that enrolled patients with anterior ST elevation or inferior elevation plus right precordial ST depression. The trial was stopped early after a large trial of pexelizumab in the setting of bypass surgery was negative. APEX AMI showed that at 30 days, there was no difference in all-cause mortality between pexelizumab and the placebo (4.1% vs. 3.9%, respectively; HR, 1.04; 95% CI, 0.80 to 1.35; $P = .78$). The composite end points of death, shock, or heart failure were also similar (9.0% vs. 9.2%, respectively; HR, 0.98; 95% CI, 0.83 to 1.16; $P = .81$). Despite the efforts to enroll high-risk patients, the surprisingly low event rate actually observed made it conceivable that the trial was underpowered to detect a treatment benefit (type II error).[106,108] However, the lack of substantial benefit of pexelizumab in patients with STEMI was recently highlighted by a meta-analysis including the COMPLY, COMMA, and APEX-AMI trials ($n = 7019$).[97] In this analysis, adding pexelizumab to mechanical or pharmacologic reperfusion did not change the rates of death (OR, 0.79; 95% CI, 0.61 to 1.03; $P = .11$), myocardial infarction (OR, 1.04; 95% CI, 0.89 to 1.22; $P = .14$), stroke (OR, 0.95; 95% CI, 0.66 to 1.38; $P = .8$), or congestive heart failure (OR, 1.0; 95% CI, 0.82 to 1.22; $P = .99$). In the same meta-analysis, pexelizumab was associated with a significant reduction in mortality when given to patients undergoing coronary artery bypass surgery (OR, 0.74; 95% CI, 0.58 to 0.94; $P = .01$), another condition of ischemia/reperfusion. This apparent contradiction might be explained by the variation in the timing of pexelizumab administration and/or varying role of complement in reperfusion injury in the two conditions.[97]

ITF-1697

ITF-1697 is a chemically modified LyS-Pro tetrapeptide (Gly-(Et)Lys-Pro-Arg) that corresponds to the sequence 113 to 116 of C-reactive protein. ITF-1697 exerts an antianaphylactic

activity[109] and has been tested in at least two distinct clinical trials on patients with MI.[110,111] While virtually no preclinical information has been formally published, before the trials came out in 2004, ITF-1697 was said to reduce reperfusion injury by preventing PMN adhesion and extravasation and by limiting the increase in vascular permeability and microcapillary plugging seen during no reflow.[110] In the Protect Against Reperfusion Injury in acute Myocardial Infarction (PARI-MI), four dose regimens of adjunctive ITF-1697 were compared with placebo in patients with AMI who were eligible for PCI. In PARI-AMI, neither a dose-relation nor a benefit could be seen in terms of infarction size, post-procedural coronary blood flow, or clinical outcome.

Emerging Anti-Inflammatory Interventions

Erythropoietin

In the past decade, our understanding of the role played by erythropoietin (EPO) has gradually shifted from a concept of strictly hematopoiesis to a broader role including anti-hypoxia.[112] Erythropoietin appears to play an important role in the development of the heart, and its defense against injury. During embryogenesis, the inactivation of the erythropoietin receptors leads to defects in cardiac morphogenesis.[113] The discovery that the cardiomyocytes express the receptor for erythropoietin has opened the way to a series of investigations to test for a protective role during ischemic stress.[114] Treatment with human recombinant erythropoietin in animal models of ischemia-reperfusion has been associated with reduced myocardial infarct size[115] and improved left ventricular functional recovery.[116,117] Erythropoietin stimulates postnatal neovascularization by enhancing endothelial precursor cell mobilization from the bone marrow.[118] Likewise, erythropoietin inhibits cardiac myocyte hypoxia-induced apoptosis through PI3K-Akt-dependent pathways,[117,119] which could favor myocardial healing. Erythropoietin also exerts a potent anti-inflammatory effect in the myocardium, where it has been shown to directly inhibit IL-6, tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein[120,121] and to block the acute inflammatory component of reperfusion injury by inducting AP-1.[122] Erythropoietin significantly reduces inflammatory cell infiltration and fibrosis in animal models of myocardial infarction[123,124] and chronic congestive heart failure.[125]

It is not known whether erythropoietin has a protective effect against ischemia-reperfusion injury in humans. Recently, high endogenous erythropoietin levels were associated with a smaller infarct size in patients treated with primary percutaneous coronary intervention.[126] The efficacy of recombinant erythropoietin is currently being tested in several small trials of patients with ACS. In a pilot study testing a single dose of epoitin-α on patients with non–ST-segment elevation ACS, no significant reduction in myocardial damage was found when compared with placebo.[127] Instead, an increase in systolic blood pressure was observed in the hours following erythropoietin (+10 mm Hg ± 16 mm Hg for epoitin vs. –6 mm Hg ± 16 mm Hg for placebo, P = .007), which is a surprising finding for a short-term therapy.[128] In patients with STEMI treated with primary PCI, a single intravenous high dose of darbepoetin alfa[129] or erythropoietin[130] was safe and well tolerated. In 2009, Binbrek and colleagues. reported on the effect of β-EPO (single 30,000 IU IV bolus before tenecteplase) compared with standard care in 236 patients admitted with STEMI within less than 6 hours of onset of symptoms. Despite EPO, the infarct size index was virtually identical in the EPO and control groups (12.4 ± 0.9 vs. 13.2 ± 0.1 creatine kinase-MB gram equivalents, respectively, data presented as mean ± SE, P = NS).[131] At discharge, the LVEF was similar in both groups. The results of this trial prompted larger confirmatory trials that are currently underway to test the effect of EPO in patients with STEMI.[132-135]

Cell Therapy

Inflammation is a putative target of cell therapy in the diseased heart. Certain cell populations may be naturally predisposed to inhibit inflammation. For instance, the mesenchymal stem cells (MSCs) have been used with apparent success in advanced inflammatory conditions, such as refractory Crohn disease[136] or steroid-resistant graft-versus-host disease.[137,138] Mesenchymal stem cells or marrow stromal cells are a rare population in the bone marrow that forms the supportive niche required by the hematopoietic tissue to maintain their function. Transplanted MSCs have been shown to down-modulate the inflammatory response in multiple experimental models,[138] including after AMI. MSCs secrete a vast array of pro-angiogenic cytokines and growth factors.[139,140] During in vivo experiments, MSCs transplanted into ischemic milieu deliver cytokines into the surrounding tissues, which is thought to favor vasculogenesis and reduce apoptosis.[141] In addition to a possible regenerative effect, the paracrine secretion of cytokines and growth factors has been proposed as one of the mechanisms for the cardioprotective effects of MSCs during ischemic injury.[123,142] MSCs do not express major histocompatibility complex class II and co-stimulatory molecules. For this reason, MSCs can directly interact with cells of the immune system to modulate the anti-inflammatory environment that can promote healing and survival of damaged cells. Whether MSCs can truly escape reaction by the immune system is controversial.[143-145] The clinical experience with MSCs on cardiac patients is limited, however.[146] Compared to placebo, the intravenous administration of heterologous MSCs (Provacel) has been associates with an encouraging protective signal in patients with recent STEMI.[147] Interestingly, a significant improvement in the forced expiratory volume in 1 second (FEV_1) was observed in all patients treated with cells, suggesting a possible anti-inflammatory lung effect. A larger trial use is currently underway to assess the efficacy of MSCs in patients with STEMI.[148]

Not every cell population seems to have beneficial anti-inflammatory effect. In the ASTAMI trial, bone marrow mononuclear cells (BMMNCs) were not superior to placebo at improving the left ventricular function following a STEMI.[149] In the study, the intracoronary injection of autologous BMMNCs resulted in a transient, yet pronounced augmentation of both the circulating IL-6 and the expression of TNF-α mRNA, along with a lesser decrease in C-reactive protein in the days following the AMI.[150] Interestingly, investigators have suggested that the improvement in cardiac function after BMMNC therapy was associated with a transient increase in myocardial infarction.[151] A better understanding of the role played by the immune system in cardiac repair following a myocardial infarction will open the way to better cell-based regenerative strategies.[152]

FX06

FX06 is a naturally occurring fibrinogen product that was initially developed as a laboratory test to monitor thrombogenesis in acute coronary syndrome.[153] FX06 is a 28-amino-acid peptide derived from the peptide sequence Bβ15-42 of human E1 fibrin fragment.[153,154] It is released by plasmin during fibrinolysis and binds to vascular endothelial (VE)-cadherin to interfere with the diapedesis of leukocytes across the endothelium.[155] The receptor for FX06 has not been identified, but the receptor CD11c expressed by neutrophils and monocytes has been proposed. In animal models of ischemia-reperfusion, FX06 has been shown to substantially reduce the circulating levels of IL-6. Likewise, it decreased the infiltration of leukocytes into the injured myocardium, therefore

reducing the infarct size and subsequent scar formation.[155,156] FX06 has a plasma half-life ranging from 11 to 17 minutes (in healthy volunteers).[156]

In the FX06 in the Prevention of Myocardial Reperfusion Injury (F.I.R.E) trial, the interplay of fibrin fragments, leukocytes and VE-cadherin was assessed in 234 patients presenting with STEMI undergoing primary PCI within 6 hours of onset of symptoms.[157] Patients were randomly assigned to either the study drug (two IV boluses; 200 mg before coronary guidewire crossed the lesion and 200 mg 10 minutes later) or their matching placebo. F.I.R.E used the infarct size at 5 days as a primary end point, measured by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), with adjustment for the rates of TIMI 0/1 flow, and the presence of collaterals before the primary PCI. Of note, the infarct size at baseline was not assessed. At 5 days, the adjusted infarct size was not different between groups (19.7% for FX06 vs. 19.8% for placebo, $P = .48$). Interestingly, a significant difference was seen in the size of the necrotic core zone (1.8 g vs. 4.2 g; $P < .025$, favoring FX06). Likewise, FX06 resulted in numerically lower rates of microvascular obstruction (27.6% vs. 37.5%, $P = .09$) measured by CMR. At 4 months, no significant differences in total LGE improvement could be seen by CMR. Overall, there were no differences across the groups in rates of treatment-related adverse events.

Cyclosporine and Analogues

Cyclosporine A has been used for decades as an immunosuppressive drug to prevent rejection after the transplantation of solid organs. Cyclosporine forms with cyclophilin D a complex that inhibits calcineurin, a potent transcription inducer of IL-2 and other lymphokines. More recently, cyclosporine and its analogues have been shown to inhibit the opening of mitochondrial permeability transition pores. The defective mitochondria are thought to play a major adverse role during reperfusion injury seen with organ transplantation.[158,159] The mitochondrial permeability transition pores are found in the inner membrane of the mitochondria. In normal conditions, these pores nonspecifically conduct low-molecular-weight solutes. During ischemia and reperfusion, the calcium and reactive oxygen species cause the pores to reopen,[160,161] resulting in mitochondrial depolarization with uncoupling of oxidative phosphorylation. The uncoupling of the respiratory chain causes the cells to become deplete in adenosine triphosphate (ATP), which leads to cell death.[161] The accompanying release of pro-apoptotic cytochrome *C* by the mitochondria may further result in cardiomyocyte death.

The pharmacologic suppression of mitochondrial permeability transition pore during ischemia and reperfusion has recently been tested in a pilot study. Piot and colleagues tested the efficacy and safety of a single cyclosporine bolus given at the time of reperfusion in patients with STEMI treated with primary PCI.[162] The size of the myocardial infarction as measured by the 72-hour CK AUC was significantly reduced in patients treated with cyclosporine, compared with placebo (relative infarct size reduction, 40%; $P = .04$). Smaller infarct sizes were also measured among cyclosporine-treated patients enrolled in the cardiac magnetic resonance substudy (relative infarct size reduction, 27%; $P = .04$). The rates of adverse clinical events were similar between the groups. At 3 months, the mean left ventricular ejection fraction as measured by echocardiography were similar in both groups (cyclosporine, 50% ± 2% vs. placebo, 47% ± 3%; $P = .32$). In the study, the blood concentration of cyclosporine was nearly undetectable in a majority of patients 12 hours after the administration of the drug.

In addition to its effect on the mitochondrial permeability transition pores, cyclosporine has additional effects that could contribute to myocardial protection during ischemia/reperfusion. In vitro, cyclosporine A appears to be effective at lowering the neutrophil chemotaxis, as well as release of toxic lysozyme and superoxide anion in response to stimulation.[163] Likewise, cyclosporine regulates the expression of inducible nitric oxide synthase (iNOS), which has been shown to protect the myocardium in ischemic conditions.[164] Proof-of-concept clinical trials with *N*-methyl-4-isoleucine cyclosporin (N1M811C), a cyclosporine analogue with no known immunosuppressive effect, will help to clarify the role played by the mitochondrial permeability transition pore during the reperfusion injury.

p38 Mitogen-Activated Protein Kinase Inhibitor

The p38 mitogen-activated protein kinase (MAPK) plays a key role in the initiation and the amplification of inflammatory processes. P38 MAPK activity increases early after myocardial infarction and appears to stay activated for several weeks thereafter.[165] In vitro, p38 MAPK has been involved in the regulation of myocyte hypertrophy and apoptosis. In experimental settings, p38 MAPK inhibition has resulted in infarct size reduction in the acute phase.[166] Likewise, it has been shown to favorably remodel the left ventricle in the chronic phase following an acute infarction.[167] Importantly, p38 MAPK inhibition has modified the atherogenic process in animal models of chronic coronary artery disease.[168] Because of its simultaneous action on the coagulation system and the inflammatory system, p38 MAPK is an appealing target for the treatment of acute coronary syndromes.

In humans, p38 MAPK has been shown to upregulate coagulation processes by increasing the expression of tissue factor on the endothelial cells and the monocytes.[166,169] In a phase I trial, oral inhibitors of the p38 MAPK attenuated the surge of circulating proinflammatory cytokines TNF-α, IL-6, and IL-8 in response to endotoxin stimulation.[170,171] Oral p38 MAPK inhibitors have been tested with limited success in chronic inflammatory conditions, such as rheumatoid arthritis and Crohn disease.[172,173] Clinical trials are under way to investigate p38 MAPK as a target for cardiovascular protection in patients with ACS.

THE CHALLENGES OF CLINICAL INVESTIGATIONS ON ISCHEMIA AND REPERFUSION

With adjunctive anti-inflammatory therapies, the discrepancy between the consistent infarct size reductions seen in animal model studies and the lack of benefits in clinical trials has raised several questions about the design and conduct of clinical research in myocardial protection, as well as the role of the inflammatory system during ischemia-reperfusion in humans.

The improvement in ACS care achieved in the last decades makes it harder to show clinical benefits with emerging therapies. For instance, mortality at 30 days as low as 4% has been observed among placebo-treated patients in a recent STEMI trial.[98] Investigators are using surrogate outcomes (principally infarct size reduction in the case of anti-inflammatory therapy) to demonstrate proof-of-principle. The duplication of the inflammatory pathways in mammals has been proposed as an explanation for the lack of benefit with single-target pharmacologic interventions. Likewise, interventions routinely used in the care of ACS patients, such as aspirin, statins,[54] and glycoprotein IIb/IIIa inhibitors,[174] modulate the inflammatory system and may, therefore, dilute the effect of new anti-inflammatory therapies.

Through the years, a number of critiques have been marshaled concerning the reliability of translational experiments to predict clinical efficacy (Table 25-3), such as failure of experimental models to recapitulate human pathophysiology

TABLE 25–3 Major Differences Between Animal Models and Clinical Studies of Patients with Acute Myocardial Infarction

Characteristic	Animal Models	Clinical Studies	Comments
Subjects	Most studies use a homogeneous group of healthy, relatively young animals free of coexisting illnesses.	Studies use heterogeneous, middle-aged patient populations with coexisting illnesses such as diabetes, hypertension, and dyslipidemia, all of which may influence cardioprotection.	Encourage the use of older animals with coexisting illnesses such as diabetes, hyperlipidemia, atherosclerosis, and hypertension to ensure cardioprotection is possible in these settings.
Medication	In most studies, the animals are receiving no other medication.	Patients may be taking different medications that may influence cardioprotection.	Ensure that patients are not receiving medication that could interfere with cardioprotection.
Period of acute myocardial ischemia	Beneficial effects with cardioprotection are observed after relatively short periods of ischemia, ranging from 30 to 60 min. The animals are subjected to the same duration and severity of ischemia.	Most patients present with longer periods of ischemia, ranging from 3 to 12 hr. Both the duration and severity of ischemia vary between patients within the same study; these factors may influence cardioprotection.	Consider selecting certain patient groups such as those presenting early (<3 hr) after symptom onset or those with an anterior myocardial infarction. Alternatively, use more clinically relevant animal models such as a human-sized pig subjected to a long period of ischemia.
Reperfusion time	Most studies assess cardioprotection after relatively short periods of reperfusion, ranging from 120 min to 3 days.	Much longer periods of reperfusion occur in patients, permitting time for the effects of infarct healing and left ventricular remodeling to take place.	Encourage the use of a longer period of reperfusion studies in animals.
Infarction model	In most studies, acute coronary occlusion is mechanically induced in healthy coronary arteries.	An acute myocardial infarction is an acute inflammatory condition. In most patients with this condition, acute coronary occlusion is due to thrombus formation at a site of a ruptured coronary atherosclerotic plaque.	Consider using more clinically relevant animal models such as animals with atherosclerotic hearts.
Intervention	Many of the interventions administered at the time of myocardial reperfusion have not shown conclusive cardioprotection.	If interventions have not shown conclusive cardioprotection in experimental studies, they are also unlikely to be cardioprotective in the clinical setting.	In the clinical setting, use only interventions rigorously shown in experimental studies to be conclusively cardioprotective. A potential approach would be the use of the intervention in a multicenter, randomized, controlled study in the animal model.*
Timing of intervention	The timing of the intervention relative to the period of ischemia and the onset of myocardial reperfusion is similar in all animals.	The timing of the intervention relative to the period of ischemia and the onset of myocardial reperfusion varies between patients. The timing of the intervention should be guided by the studies in animals.	Consider selecting certain patient groups, such as those presenting after a specific time. In clinical studies, ensure that the intervention is administered before myocardial reperfusion.
Infarct size	Varies from 30% to 60% of the total volume of myocardium at risk, providing a greater scope for cardioprotection.	Infarct sizes of 13% to 16% expressed as a percentage of left ventricular volume (using SPECT) appear to be the normal range, which may limit the scope for cardioprotection.	Encourage the use of more accurate measurement of infarct size using delayed-enhancement cardiac magnetic resonance imaging, which can express infarct size as a percentage of the ischemic risk area.
End points for cardioprotection	Most studies use recovery of left ventricular function or myocardial infarct size as the measured end points.	The clinically relevant end points are outcomes such as short-term and long-term effects on illness and death.	Consider more robust end points in studies in animals, such as long-term effects on left ventricular function and death.

*Data from Bolli R, Becker L, Gross G, et al: Myocardial protection at a crossroads: The need for translation into clinical therapy. Circ Res 2004;95:125-134, and Baxter GF, Hale SL, Miki T, et al: Adenosine A1 agonist at reperfusion trial (AART): Results of a three-center, blinded, randomized, controlled experimental infarct study. Cardiovasc Drugs Ther 2000;14:607-614.

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and the lack of co-morbidities in animals. In senescent mice, the suppressed inflammation has been associated with a delayed formation of the granulation tissue and adverse post-infarction remodeling.[152] The young animals used in most translational experiments may not accurately reflect the pathologic process encountered in older human adults. In addition, the presence of chronic inflammatory conditions in humans could blunt the efficacy of the investigational drug seen in animals.[175]

The ischemia and reperfusion model used in animals generally employs a mechanical occlusion of the coronary artery, which does not involve activated platelets and thrombosis, critical components of the inflammatory reaction. This acute mechanical coronary occlusion in animals may not adequately replicate the clinical reality where many patients experience preconditioning angina[176] or have extensive collateral networks.[177] Finally, the time-limited mechanical occlusions used in translational models (typically 45 to 60 minutes) differs from the sustained (or dynamic) thromboembolic[178] occlusion experienced in the clinic, which typically lasts more than 2 hours.[98] Recently, there has been a call for translational studies analogous to clinical trials, where mammals (including primates) would be randomized to blinded studies throughout a network of independent

investigators.[6,179,180] Only once multicenter studies suggest a benefit would the investigational drug move to a phase 1 clinical trial.

In terms of efficacy, it remains unclear what end point is the most appropriate to use when studying myocardial protection. The variation in infarct size before and after administration of study drug is regarded as an appropriate surrogate outcome because it represents the putative mechanism of action for most adjunctive anti-inflammatory drugs. Interestingly enough, one adjunctive anti-inflammatory agent that successfully reduced infarct size[67] did not reduce the occurrence of death, CHF, and rehospitalization in a larger trial.[68] The reasons for this finding are unclear, but could constitute insufficient power to show an effect in the phase III trial. Compared with the nuclear medicine SPECT analysis, the superior spatial resolution of CMR will likely improve the ability to detect a significant intergroup infarct size difference in trials to come.[181] One problem that remains with the use of imaging for infarct size quantification is the lack of a true baseline infarct size measurement in most clinical investigations. For practical and safety reasons, most infarct size quantifications are done between day 5 and 9 after the infarction.[182] Myocardial necrosis markers (area-under-the-curve) can augment imaging techniques by providing complementary information.

Pharmacology may provide assistance in understanding the neutral results observed with adjunctive anti-inflammatory agents. Most anti-inflammatory study drugs are administered over a short period compared with the relatively long-term inflammatory reaction following an AMI. In some cases, a single intracoronary bolus is given at the time of reperfusion. This may be insufficient to provide a sustained protection and an overall benefit. The benefit of inflammatory modulation may or may not be concentrated in the critical period when most of the myocardial salvage is thought to occur (in the 2 to 6 hours following the onset of symptoms).[183] The reason for a longer window of opportunity for an anti-inflammatory strategy is that the immune and the inflammatory systems are involved in healing of the infarcted ventricles. In terms of pharmacokinetics, it is generally assumed that the myocardium is a distinct compartment where drugs distribute uniformly. It has been hypothesized that the necrosis seen during AMI leads to failure of natural barriers, such as the rupture of the endothelial cell barrier.[87] Under this hypothesis, the injured myocardium is no longer a unique compartment but is instead open to a much wider volume of distribution. The time-limited mechanical occlusions used in translational models may not adequately replicate the rupture of the endothelial barriers thought to occur in humans.

Controversies Surrounding the Nature of Reperfusion Injury in Humans

Apart from the modulation of the immune-inflammatory systems, other approaches have been tested to protect the myocardium during ischemia/reperfusion, including the reduction of the harmful intracellular calcium, the inhibition of apoptosis, and the enhancement of oxygen delivery.[5] In face of the uniformly neutral clinical trials, the existence and the nature of the reperfusion injury in human myocardial infarction have been questioned. Apart from the limitations of the translational and clinical trials cited above, the importance of reperfusion injury on cardiomyocytes may have been overstated. Whether reperfusion injury independently causes cell death has been controversial since the concept was originally proposed. In a classic experiment, Zahger and coworkers could not demonstrate any signs of reperfusion injury after simultaneously subjecting the same animals to infarctions with and without reperfusion.[184,185] In the model used, the distal left anterior descending (LAD) coronary artery was first bypassed by a shunt from the left carotid artery. The LAD artery was thereafter occluded simultaneously in its proximal and its mid portion, just above the insertion site of the shunt. The shunt was also temporarily blocked to prevent perfusion of the distal LAD. After 180 minutes of LAD occlusion, the arterial shunt was reopened and therefore allowed a selective reperfusion of the distal LAD while leaving the proximal LAD segment non-reperfused. This model had the advantage of eliminating most of the variability in collateral blood flow usually seen between subjects.

The role played by neutrophils in the reperfusion injury has also been debated for a long time.[186,187] One of the strongest arguments against neutrophils derives from the fact that reperfusion injury can be seen in neutrophil-free systems, such as isolated heart preparation.[14] The disappointing results of the recent clinical investigations have led many to hypothesize that the early inflammatory response caused be reperfusion may not be harmful, and may in fact be a desirable, essential step for optimal cardiac healing.[152] An increasing number of publications are revisiting the contribution of inflammation as an adaptive mechanism en route to tissue preservation and timely cardiac repair.[14,188]

FUTURE DIRECTIONS

Beyond the numerous inflammatory targets that are likely to be investigated in the future, better patient selection and innovative ways to deliver the anti-inflammatory therapy will possibly offer venues for the use of adjunctive anti-inflammatory therapy in patients with ACS. Better understanding of the timing of various aspects of the inflammatory response, its relationship to further damage, and its relationship to healing is needed.

Personalized medicine holds the potential to redefine how we study newer anti-inflammatory drugs. In 2004, an Icelandic group identified gene variants encoding for the 5-lipoxygenase-activating protein (*FLAP, ALOX5AP*) that was associated with an almost 2-fold increased risk of myocardial infarction in the general population.[189] In the leukotriene pathway, *FLAP* leads to the production of leukotriene B_4, which is a mediator of inflammation.[190] The effect of *FLAP* inhibition in MI patients carrying the at-risk variants of the *FLAP* gene was subsequently studied in a small pilot randomized placebo-controlled study. Administration of the FLAP inhibitor DG-031 for 4 weeks led to significant and dose-dependent suppression of the inflammatory biomarkers that are associated with increased risk of MI events.[191] This small cohort trial suggested for the first time that some success could be achieved with anti-inflammatory adjunctive therapies by customizing targets based on the patient's genotype. The same group subsequently identified a haplotype for the *LTA4H* gene (encoding the leukotriene A_4 hydrolase), which confers a substantial risk of myocardial infarction in African Americans.[192]

Better ways to deliver the study drug may constitute an interesting option for certain drugs. Among the different explanations provided for why adjunctive anti-inflammatory drugs have not translated into clinical benefits, one possibility is that the study drug delivered through the coronary artery or the intravenous route does not adequately reach the target myocardium. After a primary percutaneous coronary intervention, the myocardial tissue may not be actually reperfused despite the restoration of a TIMI 3 flow in the infarct-related artery.[193] Novel routes of administration, such as the coronary sinus, may provide promise.[194] The coronary sinus is the main venous structure that drains blood coming from the coronary arteries and has been known for years to be a possible route to deliver therapies directly to the heart.[195,196]

Proof-of-concept studies have shown pronounced and homogeneous tissue accumulation of drugs delivered through the coronary sinus.[197,198] The lack of a so-called resistance vessel between the coronary sinus and capillaries has been offered as an explanation as to why retrograde infusion could yield a superior myocardial biodistribution.[199] This could be useful to assure the delivery of therapies to the target myocardium during myocardial infarction. The coronary sinus can generally be cannulated with minimally invasive techniques.[194] The retroinfusion of cardioprotective substances in the coronary sinus has been done safely in humans, in selected clinical settings.[200]

Ultimately, expansion of therapies for myocardial infarction to improve the tolerability of the myocardium to ischemia/reperfusion and to enhance myocardial recovery provides important opportunities to improve patient care.

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CHAPTER 26

Plaque Passivation and Endothelial Therapy

Peter L. Thompson

The central role of the unstable plaque and disturbed endothelial function in acute coronary syndromes is described in Chapters 6 and 17. This chapter briefly reviews these mechanisms and the potential for reversing them in patients with acute coronary syndromes. Several therapies proven to be beneficial in improving outcomes in acute coronary syndromes may act by acute stabilization of the unstable plaque and reversal of endothelial dysfunction and likely future therapies are discussed.

THE CONCEPT OF PLAQUE PASSIVATION

The pathophysiologic processes that contribute to instability of the coronary atherosclerotic plaque are now well described,[1,2] and there has been considerable progress in understanding the causes of inflammation and its consequences.[3] A vulnerable plaque is characterized by an increased lipid pool, an increased macrophage, foam cell and T-lymphocyte content, and reduced collagen and smooth muscle cell population.[4,5] This can lead to rupture or erosion at the margins or shoulder region of the plaque where the overlying fibrous cap is thinnest and infiltrated by macrophages[6] and exposed to the greatest shear stress.[7,8] Current practice employs aggressive antithrombotic strategies to stabilize the patient with an acute coronary syndrome by targeting platelet adhesion, aggregation, and thrombosis in the coronary arteries. In contrast to the relatively advanced state of antithrombotic therapies, there is at present a paucity of validated diagnostic tools to identify the unstable plaque and only a few clearly identified therapeutic targets for preventing plaque rupture and enhancing plaque stabilization (see Chapter 18). Nevertheless, there is a huge potential to improve clinical outcomes in acute coronary syndromes if the balance of the complex processes within the unstable plaque can be tipped toward endothelial stabilization and passivation of the unstable plaque.

Multiple factors determine the balance between instability and stability of the atherosclerotic plaque and define the potential therapeutic targets. The factors affecting the balance between stability and instability of the plaque are summarized in Box 26-1.

These include the thickness of the overlying fibrous cap, the function of the vascular smooth muscle cells, the extent of the inflammatory process, the size of the lipid pool, and matrix degeneration by metalloproteinases.

Thickness of the Overlying Fibrous Cap

Histopathologic observations confirm that a thin overlying cap is a typical feature of the unstable plaque, leading to rupture and erosion.[6] Both rupture and erosion are important and shear stresses may mechanically damage the endothelium without rupture occurring.[9] Therefore, plaque will be strengthened by deposition of collagen in the fibrous cap, and vice versa. Controlling this process in the unstable plaque without encouraging adverse vascular remodeling and without affecting matrix synthesis in other tissues and organs is a significant challenge.

Function of Vascular Smooth Muscle Cells

Smooth muscle cells have the capacity to modulate their phenotype from normal contractile cells to a synthetic phenotype capable of proliferation and enhanced matrix synthesis.[10] Transition to the synthetic phenotype of smooth muscle cells is associated with an increase in collagen secretion, a key process in enhancing plaque stabilization.[11] In contrast, the unstable atherosclerotic plaque is typically characterized by reduced numbers of vascular smooth muscle cells and reduced collagen content, and an increase in the rate of smooth muscle cell apoptosis. The rate of apoptosis is a major determinant of the numbers of vascular smooth muscle cells in the atherosclerotic plaque and is governed by complex cell, cell matrix, and cell cytokine interactions.[12] There is evidence of increased apoptosis of vascular smooth muscles in the atherosclerotic plaque of unstable angina patients compared with stable angina

BOX 26-1 Potential Targets for Plaque Stabilization and Passivation

Thickness of the overlying fibrous cap
Synthetic role of vascular smooth muscle cells
Extent of the inflammatory process
Size of the lipid pool
Matrix degeneration by metalloproteinases

patients,[13] and apoptosis has been detected in the shoulder region of plaques at the sites that appear most likely to rupture.[14] The expression of nitric oxide (NO), enhanced by cytokines such as interleukin-1 beta, interferon gamma, and tumor necrosis factor involved in the inflammatory process[15] and acting via the production of peroxynitrite in combination with superoxide radicals, is a key determinant of the rate of smooth muscle cell apoptosis. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) may have a role modulating the apoptotic processes that lead to plaque instability by stimulating macrophage apoptosis and encouraging the ingrowth of vascular smooth muscle.[16] TRAIL levels are reduced in acute coronary syndromes and human recombinant TRAIL has been shown to ameliorate atherosclerosis in mice.[17]

Extent of the Inflammatory Process

Atherosclerosis has been recognized as an inflammatory process,[3] and unstable plaques in particular are characterized by a dense inflammatory cell infiltrate.[6] Atherectomy specimens from patients with acute coronary syndromes show an increased frequency of macrophages and T lymphocytes compared with atherectomy specimens of patients with refractory unstable angina.[18] Control of the inflammatory cell infiltrate into an unstable atherosclerotic plaque by modulation of cell adhesion molecules and migration factors is a potential approach to stabilizing the unstable plaque.

Size of the Lipid Pool

In addition to the thickness of the overlying cap and the degree of cellular infiltration, the degree of stability of the plaque is determined by the size of the lipid pool. Davies and coworkers established that the critical threshold of vulnerability to rupture was a 50% volume of extracellular lipids.[19] Computer modeling of plaques has identified the circumferential tensile strength on the fibrous cap as the most important mechanical stress factor involved in plaque rupture.[20,21] Therefore, any intervention that can reduce the size of the lipid pool is likely to stabilize the plaque.

Matrix Degeneration by Metalloproteinases

Matrix degradation leading to plaque rupture appears to be primarily due to the action of matrix metalloproteinases (MMPs).[22] MMPs expression by vascular smooth muscle cells and macrophages is increased in human atherosclerotic plaques.[23] The activity of MMPs is inhibited by naturally occurring tissue inhibitors of metalloproteinases (TIMPs). Exogenously administered TIMPs are readily metabolized and denatured.[24]

ROLE OF ENDOTHELIUM AND ENDOTHELIAL DYSFUNCTION

The vascular endothelium is the most widely distributed but largest "organ" in the body equivalent in area to a football field and in mass to five normal-sized hearts. Endothelial cells line the cardiovascular system and provide an interface between blood and tissues linked by tight junctions allowing intercellular communication and exchange of solutes and ions. In addition, the endothelium has complex functions, which modulate smooth muscle tone, mediate hemostasis, cellular proliferation, and inflammatory and immune mechanisms in the vessel wall.[25] Furchgott's seminal observations established that normal vasoregulation requires the presence of the endothelium.[26] The modulation of vascular tone is dependent on relaxing and contracting factors derived from the endothelium. These are summarized in Box 26-2.

BOX 26-2 Endothelial-Dependent Vasoactive Substances

Endothelium-dependent vasodilation
Prostacyclin (PGI_2)
Endothelium-derived relaxation factor (EDRF), nitric oxide (NO)
Endothelium-derived hyperpolarizing factor (EDHF)

Endothelium-dependent vasoconstriction
Eicosanoid family (especially thromboxane A_2)
Endothelin-1

Endothelium-Dependent Vasodilation. This is dependent on at least three endothelium-derived vasodilators, each of which represents a potential therapeutic target. The first is the potent endothelium-derived vasoactive substance *prostacyclin (PGI_2)*, discovered in the late 1970s.[27] A more labile, diffusible substance which mediated endothelium-dependent vasorelaxation, was discovered in the 1980s,[28] referred to initially as *endothelium-derived relaxation factor (EDRF)*, is now well established as *nitric oxide*.[29,30] Nitric oxide is synthesized from its precursor, L-arginine, with the enzyme nitric oxide synthase. There are three isoforms of nitric oxide synthase, neuronal n-NOS, inducible i-NOS, and endothelial e-NOS,[31] of which e-NOS is expressed ubiquitously in endothelial cells, and differing genotypes offer some potential for gene therapy.[32] The activity of nitric oxide is dependent on an intracellular rise in calcium which is signaled through stimulation with neurotransmitters such as acetylcholine or substance P, circulating hormones such as bradykinin, or shear stress. A third vasodilating factor referred to as *endothelium-derived hyperpolarizing factor* (EDHF), which leads to hyperpolarization of smooth muscle cells via activation of potassium channels, has been identified.[33]

Endothelium-Dependent Vasoconstriction. Vasoconstriction is mediated by two directly acting endothelium-derived contracting factors, the eicosanoid family, predominantly thromboxane A_2, and the endothelins.[34] The endothelin most active in the vasculature is endothelin-1, stimulated by numerous endogenous agents including interleukin-1, transforming growth factor beta, shear stress, and hypoxia. Vasoconstriction is also enhanced by the final stage of production of angiotensin II by the angiotensin-converting enzyme at the luminal surface of endothelial cells.[35]

In addition to its role in vasoregulation, the endothelium secretes a range of prothrombotic and antithrombotic factors including tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI1). The endothelium helps prevent spontaneous platelet aggregation adhesion by production of prostacyclin and nitric oxide.

The endothelium contains important mechanoreceptors that sense changes in shear stress and hydrostatic pressure; flow-induced vessel dilatation requires an intact functional endothelium[36] and is the basis of the widely used flow-mediated dilatation test of endothelial function.[37]

The concept of endothelial dysfunction has been intensively studied.[38] Endothelial cells are activated by the inflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor-α, and interferon-γ. Activated endothelial cells express leukocyte adhesion molecules and produce tissue factor, creating a procoagulant environment. Endothelial cell injury results in a dysfunctional endothelium, which can no longer maintain a thromboresistant state and promotes vasoconstriction by diminished production of nitric oxide and synthesis of endothelin-1.[38] The production of reactive oxygen species as a consequence of endothelial injury potentiates endothelial dysfunction by depleting available NO and reacting to form peroxynitrite, which causes further oxidative injury to the endothelium. The production of lipid peroxides further depletes NO.[39] Oxidized low-density lipoprotein (LDL) acts as chemoattractant for macrophages, which in turn promote the expression of adhesion molecules on the endothelial surface.[40] Reversal of endothelial dysfunction is an important future target of therapy in patients with acute coronary syndromes (ACS), while some of the interventions currently used for ACS achieve their benefit by reversing endothelial dysfunction. These are discussed later.

TABLE 26–1 Trials of Early Initiation of Statins in Acute Coronary Syndromes

Trial	Time of Commencement	*N*	Drugs	Patients
MIRACL[61]	24-96 hours	3086	Atorvastatin 80 mg Placebo	NSTEMI
PACT[65]	<24 hours	3408	Pravastatin 20-40 mg vs. placebo	STEMI and NSTEMI
A to Z[64]	<5 days, mean 3.7 days	4497	Tirofiban then simvastatin 40 mg vs. placebo	NSTEMI
PROVE-IT[63]	<10 days median 7 days	4162	Pravastatin 40 mg vs. atorvastatin 80 mg	NSTEMI
FLORIDA[62]	Median 8 days	540	Fluvastatin 80 mg vs. placebo	AMI

NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

THERAPIES DIRECTED TO PLAQUE STABILIZATION AND CORRECTION OF ENDOTHELIAL DYSFUNCTION

Reduction of Low-Density Lipoproteins (LDL)—Hydroxy-methylglutaryl Coenzyme A Reductase Inhibitors (Statins)

Statins have been demonstrated to influence a number of other mechanisms independent of their lipid-lowering effects that are thought to be potentially important in the treatment of acute coronary syndromes. Animal studies have revealed potential roles for statins in plaque stabilization, by increase in collagen content of the unstable plaque,[41] reduced macrophage activation and expression of matrix metalloproteinases,[42] and modulation of immune function. Reductions in plasma fibrinogen[43] and thrombogenic factors have been demonstrated in hypercholesterolemic patients.[44,45] A tendency for enhanced platelet thrombus formation in subjects with hypercholesterolemia can be reversed with only 2.4 months of treatment with pravastatin.[46] Early improvements in endothelial-dependent vasodilation have been demonstrated in hypercholesterolemic patients,[47-50] and these benefits have been confirmed within 6 weeks of commencing statin therapy in patients who are recovering from an acute coronary syndrome.[51]

Clinical trials in patients stabilized *after* a coronary event have demonstrated beyond doubt that treatment with statins reduces the risk of future cardiovascular events and reduces mortality in patients with cardiovascular disease.[52-54] While it would seem logical to initiate secondary preventive treatment as soon as possible after the acute event,[55] the "evidence gap" to judge whether there is truly an early effect of statins in acute coronary syndromes has recently narrowed.

Small-scale clinical trials showed that statins started 2 to 10 days after acute myocardial infarction (AMI) or unstable angina pectoris (UAP) were well tolerated and associated with reductions in total and LDL cholesterol and improvements in endothelial function.[56,57] These early studies did not assess long-term outcomes.

Retrospective analyses of databases suggested a beneficial short-term effect of statin therapy prior to or immediately following admission to hospital with AMI.[58-60] Despite the use of sophisticated matching techniques for assessing the propensity for being prescribed lipid-lowering therapy in these observational studies, the possibility of bias in the decision to treat could not be excluded, and the effect of statins could not be separated from the effect of other lipid-lowering therapies. Randomized trial data to fully assess the impact of early statin therapy has recently become available.

The randomized clinical trials of early commencement of statins after a coronary event and the meta-analyses of these trials are summarized in Table 26-1.

The MIRACL study was the first large-scale clinical trial completed to investigate whether early treatment with a statin in patients with UAP or a non–Q-wave AMI is beneficial.[61] MIRACL enrolled 3086 patients with UAP or non–Q-wave acute MI within 24 to 96 hours of hospital admission for randomization to atorvastatin 80 mg per day or placebo. The primary efficacy parameter was time at the first occurrence of death, resuscitated cardiac arrest, non-fatal MI, or angina pectoris with evidence of myocardial ischemia requiring re-hospitalization. The relative risk (RR) of the primary efficacy measure was 0.84 ($P = .048$, 95% confidence interval [CI], 0.701-0.999), and for re-hospitalization for UAP (a component of the primary efficacy measure) was 0.74 ($P = .02$, 95% CI, 0.57-0.95). There was no effect on death, non-fatal myocardial infarction, or resuscitated cardiac arrest. An unexpected halving of the stroke rate from 1.6 to 0.8 ($P = .05$, 95% CI, 0.026-0.99) was observed. The primary efficacy measure in the MIRACL trial only just achieved its statistical significance, and the results were not definitive evidence of an early benefit for statins in the modern treatment of acute coronary syndromes.[62]

The PROVE-IT trial compared the effect of a moderate statin regimen of pravastatin 40 mg with aggressive regimen of atorvastatin 80 mg, in 4162 patients who had been hospitalized for an ACS within the preceding 10 days. The trial showed a significant benefit of the more aggressive statin regimen with a 16% reduction in the hazard ratio (HR) in favor of atorvastatin ($P = .005$, 95% CI, 5%-26%).[63]

The A to Z study studied the effect of statin therapy (simvastatin) in stabilizing the postcoronary course in patients who had received a glycoprotein (GP) IIb/IIIa inhibitor (tirofiban) in the early treatment of their ACS. The trial compared 2265 ACS patients who received 40 mg/day of simvastatin for 1 month followed by 80 mg/day thereafter with 2232

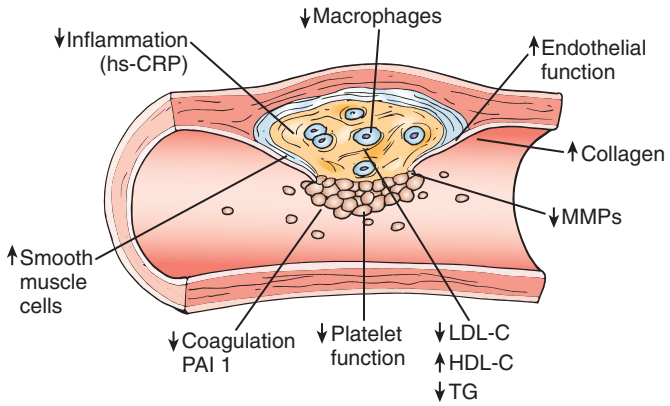

FIGURE 26–1 Potential effects of statins on unstable plaque.

patients receiving placebo for 4 months followed by 20 mg/day of simvastatin. There was not a statistically significant difference in the composite primary end point of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke during the first 4 months between the groups for the primary end point (HR, 1.01; 95% CI, 0.83-1.25; P = .89), but from 4 months through the end of the study the primary end point was significantly reduced in the higher dose simvastatin group (HR, 0.75; 95% CI, 0.60-0.95; P = .02).[64] The results of this trial were confounded by a relatively high incidence of myopathy in patients receiving simvastatin 80 mg/day, compared with patients receiving lower doses of simvastatin (P = .02).

Two studies have commenced the statin within 24 hours of onset of an acute coronary syndrome. The FLORIDA trial compared very early fluvastatin 80 mg daily with placebo. In 545 patients, the statin did not affect ischemia on ambulatory electrocardiography (AECG), nor the occurrence of any major clinical events as compared to placebo, but the trial was underpowered because the prevalence of unstable ischemia was low. The PACT trial initiated statin therapy even earlier, within 24 hours after the onset of the acute coronary syndrome, and its primary end point was the frequency of events within the first month. The trial was stopped before the anticipated 10,000 patients were enrolled, but a total of 3408 patients were randomly assigned to treatment with pravastatin or matching placebo. Treatment was continued for 4 weeks; a relative risk reduction of 6.4% favored allocation to pravastatin but was not statistically significant (95% CI, 13.2%-27.6%).[65]

The timing of commencement of therapy in the published trials of statins after acute coronary syndromes is summarized in Figure 26-1.

Meta-analysis of the trials of early statins in acute coronary syndromes did not show any benefit on early outcomes. Death, stroke, cardiovascular death, fatal or nonfatal myocardial infarction, or revascularization procedures were not reduced in the first 4 months[66]; however, there were effects on extended follow-up, which started to appear at 4 months and continued for at least 2 years.[67] The dose of statin required to achieve benefit is high, as demonstrated in the PROVE-IT trial, which showed that the benefit of 80 mg atorvastatin was superior to 40 mg of pravastatin. A meta-analysis of safety data for high dose versus low dose statin has not shown any adverse effect.[68] On the basis of these recent trials, the evidence that early initiation of statins is regarded as level A and in recent guidelines, initiation in hospital is recommended.[69] In summary, there are valid reasons, including convenience and no evidence of an adverse effect, for initiating aggressive LDL-lowering therapy with a statin in hospital after an acute coronary syndrome.

Further evidence that statins may have a direct plaque-stabilizing effect independent of their lipid-lowering effects comes from studies that have shown improved outcomes with statin pre-loading[70,71] and re-loading[72] immediately prior to percutaneous coronary intervention.

Raising High-Density Lipoprotein (HDL)

The possibility that the benefits of LDL reduction by statins could be potentiated by raising endogenous HDL levels or with HDL mimetics has been explored, but to date has not reached the point of clinical application. The ILLUMINATE trial of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib was aborted because of an increase in all-cause mortality, and this has stimulated debate on whether raising HDL will be beneficial in acute coronary syndromes, or whether the adverse effects in the ILLUMINATE trial were due to a molecule-specific effect on raising blood pressure.[73] Several alternative methods of raising HDL are under investigation.[74] A trial of infusion of APO A-1 Milano in acute coronary syndrome patients resulted in a significant reduction in atherosclerosis volume measured by intravascular ultrasound.[75] A trial of recombinant HDL in acute coronary syndromes has been completed and showed no benefit on atherosclerosis volume.[76] Further trials are underway in acute coronary syndromes with recombinant HDLs and HDL mimetics and alternative targets for raising HDL.[77]

Angiotensin Converting Enzyme (ACE) Inhibitors

The presence of an important tissue renin-angiotensin system is now well recognized, and it is estimated that less than 10% of ACE is found circulating in the plasma.[78] The central role of the system in the vascular wall is summarized in Figure 26-2.

Angiotensin II can have a wide range of deleterious effects in the vascular wall, including vasoconstriction by stimulating the production of norepinephrine and enhancing the production of endothelin-1, which further facilitates the conversion of angiotensin I to angiotensin II. It also promotes the release of inflammatory cytokines, thrombotic factors, and metalloproteinases. The endothelial-based receptor that binds oxidized LDL (lectin-like Old receptor type 1, [LOX]) interacts with angiotensin II. Angiotensin II upregulates the receptor effects, which can be blocked with angiotensin receptor blockers and angiotensin converting enzyme inhibitors.[79] ACE inhibitors can block these effects, shifting the balance in favor of vasodilatation, anti-inflammatory, and antiproliferative effects.

These effects have been demonstrated to be clinically significant.[80,81] Several clinical trials of ACE inhibitors have shown improvements in coronary endothelial dysfunction in patients with coronary artery disease. Quinapril 40 mg per day partly reversed the vasoconstricting effects of intracoronary acetylcholine in patients with coronary artery disease[82]; however, the effects on atherosclerotic progression were less impressive.[83]

The benefits of ACE inhibitors on improving ischemic outcomes has been the subject of detailed study in patients with stable coronary artery disease and those at high risk, but have not been tested directly in the setting of acute coronary syndromes. A benefit on ischemic events in chronically treated patients suggests mechanisms of benefit on coronary atherosclerosis independent of the well established benefits in hypertension and cardiac failure and left ventricular dysfunction. This was initially suspected in retrospective analyses of the cardiac failure and postinfarction trials, which showed effects consistent with a benefit on myocardial ischemia, in addition to the hypothesized effect on left ventricular dysfunction.[84-86] Randomized trials of ACE inhibitors in

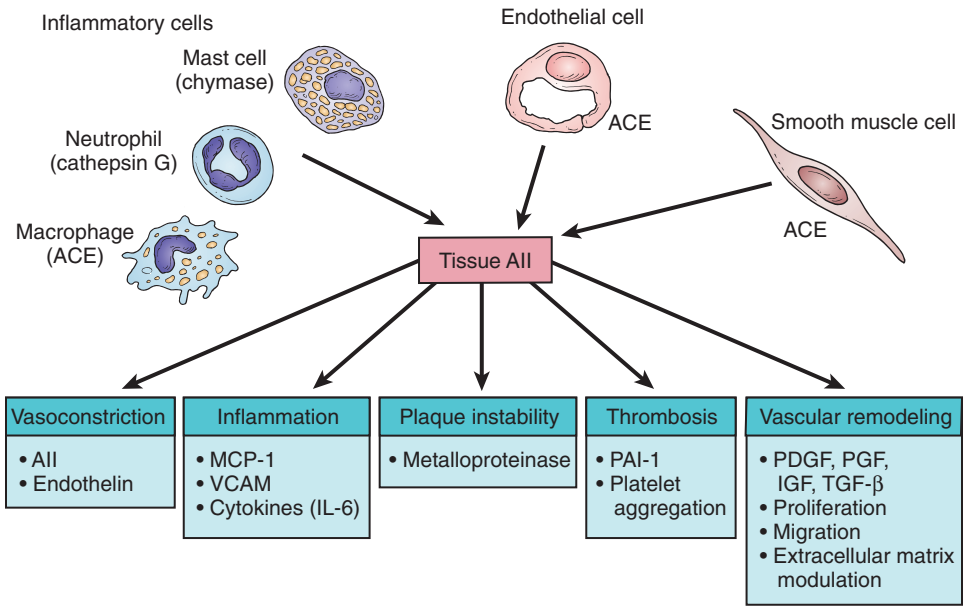

FIGURE 26–2 Effects of the tissue angiotensin system on the vessel wall. *(Modified with permission from Dzau VJ, Bernstein K, Celermajer D, et al; Working Group on Tissue Angiotensin-converting enzyme, International Society of Cardiovascular Pharmacotherapy: The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. Am J Cardiol 2001;88:1L-20L; Figure 4.)*

patients with preserved left ventricular function have shown a reduction in the rates of mortality and vascular events in high-risk patients including many diabetics (HOPE trial)[87] and in high-risk postinfarction patients (EUROPA trial).[88] There was no benefit demonstrated in lower risk patients (PEACE trial).[89] A subsequent meta-analysis of these three major trials supported benefit of ACE inhibition even in patients at low risk.[90] There are no modern data in acute coronary syndromes, and extrapolations from stable patients may not be relevant. It is not yet clear if these benefits of ACE inhibitors on endothelial function will be mimicked by the angiotensin II receptor antagonists (AIIRAs, ARBs). A preliminary study with irbesartan suggests that it has effects on cytokines and adhesion molecules in patients with premature atherosclerosis, which may be of potential benefit in plaque passivation and restoration of endothelial dysfunction.[91]

The CHARM Preserved study of inpatients with preserved left ventricular function showed no effect on mortality or on composite outcomes, which included nonfatal myocardial infarction and nonfatal stroke,[92] and a large scale trial (ONTARGET) in stable patients with coronary heart disease showed no difference in effect between the ACE inhibitor ramipril and the angiotensin receptor blocker telmisartan.[93] The use of ACE inhibitors during acute coronary syndromes and myocardial infarction is well supported by randomized clinical trials but the benefit is less dramatic in those without left ventricular dysfunction,[94] and the current data does not necessarily support the routine use of ACE inhibitors in patients with acute coronary syndromes.[95] Caution in the use of ACE inhibitors early in acute coronary syndromes is necessary and it should be recalled that the first trial of an ACE-I in acute myocardial infarction had an adverse effect due to hypotension.[96]

Aspirin–Angiotensin Converting Enzyme (ACE) Inhibitor Interaction?

Several studies have suggested that patients taking aspirin concomitantly with ACE inhibitors will have a reduced effectiveness of the ACE inhibitor benefit because of the inhibition of prostaglandins by the aspirin.[97,98] However, there was no evidence of a clinically significant interaction potential in overviews of all the large postinfarction trials.[99,100] In view of this evidence in large scale trials, it seems unlikely that this interaction would be significant in the setting of combined aspirin and ACE inhibitor use in ACS. However, an analysis of the combination in patients in acute coronary reperfusion studies and trials of antiplatelet therapy in patients undergoing percutaneous coronary intervention have suggested an interaction.[101] After adjusting for confounders, combined use of aspirin and ACE inhibitors was associated with increased mortality compared with aspirin alone. Despite the reassuring findings from the large trials in stable patients, the possibility of an interaction during the intensive therapy phase of an acute coronary syndrome cannot be discounted.

IMMUNOMODULATION FOR PLAQUE STABILIZATION

Directly targeting the inflammatory process in the unstable plaque is a logical approach, but not yet a proven therapeutic strategy.

The role of C-reactive protein (CRP) in provoking instability in atherosclerosis remains a hotly disputed area of research.[102] CRP has been identified in the unstable plaque and can upregulate cytokine,[103] cell adhesion molecule,[104] and matrix metalloproteinase expression,[105] all factors that are implicated in instability of the atherosclerotic plaque, and can also activate the CD40/CD40 ligand, an important link between atherosclerosis and thrombosis.[106] Because of these observations, there has been keen interest in identifying inhibitors of CRP, which may have a role in stabilization of the unstable atherosclerotic plaque. There are many potential CRP inhibitors, but it is worth noting that the demonstration that circulating CRP levels are lowered by an intervention does not necessarily imply an inhibition of the molecular action of CRP nor does it necessarily imply benefits on atherosclerosis. CRP may simply be a marker that inflammation is present. For instance, rofecoxib lowers hs-CRP significantly, and was suggested as a possible candidate for trial of

the atherosclerosis/inflammatory hypothesis only weeks before the worldwide withdrawal of rofecoxib because of adverse vascular effects.[107] A molecule that directly targets *CRP* has been developed and recently reported.[108] 1,6-Bis(phosphocholine)-hexane is a specific small-molecule inhibitor of CRP, which has been shown in rats undergoing acute myocardial infarction to abrogate the increase in infarct size and cardiac dysfunction produced by injection of human CRP. There are no data yet on effects on atherosclerosis, and its role in stabilizing the atherosclerotic plaque will depend on the outcome of the debate on whether CRP has a direct adverse effect on the vascular wall.

Specific inhibitors of cytokines involved in the inflammatory cascade "upstream" from CRP release from the liver are available for patients with inflammatory conditions such as rheumatoid arthritis.

Inhibitors of tumor necrosis factor (TNF-α), which have been shown to reduce inflammation are in clinical use in rheumatoid arthritis, but examination of their role in atherosclerotic vascular disease has been limited. The TNF-α inhibitor etanercept has shown a clear effect on CRP in metabolic syndrome[109] but trials of the effect on modulating the inflammatory state in cardiac failure patients resulted in adverse effects and early termination of the trials.[110] Furthermore, TNF-α inhibition has other non-vascular effects on inflammation, which may limit the suitability for use in atherosclerosis. A meta-analysis of the effect in 3493 patients with rheumatoid arthritis who received anti-TNF-α antibody treatment and 1512 patients who received placebo showed worrying increases in malignancy (odds ratio [OR] 3.3; 95% CI, 1.2-9.1) and serious infection (OR 2.0; 95% CI, 1.3-3.1). Malignancies were significantly more common in patients treated with higher doses.[111] The role of selective inhibitors of IL-6 has been examined in inflammatory diseases[112,113] but to date, not in atherosclerosis. IL-1 is released early in the process of plaque instability and may be amenable to inhibition by a specific blocker, and a trial to test the effect on inflammatory markers in ACS is currently underway.[114]

Since MMPs have been implicated in the process of plaque destabilization, TIMPs may have a future role.[115] A specific inhibitor of MMP 9 has been shown to be ineffective in preventing adverse remodeling post myocardial infarction,[116] but its role in plaque stabilization has not been evaluated. The role of CD40 ligand (also known as CD154) in contributing to plaque instability has been well studied. The CD40 pathway is a key signaling mechanism through which macrophages and vascular smooth muscle cells in atheroma can express matrix-degrading proteinases leading to plaque rupture.[117]

Interruption of the CD40-CD40 ligand interaction raises the intriguing therapeutic possibility that interruption of CD40 signaling by a CD40 ligand antibody could result in plaque stabilization,[118,119] but clinical trials directed to this target have not yet been conducted.

Lipoprotein-associated phospholipase 2 (PL-PLA2) is produced primarily by macrophages and lymphocytes and is bound to LDL; it has been shown to be proinflammatory and atherogenic. A promising immunomodulating approach to plaque instability may be to inhibit LP-PLA2 by a selective inhibitor (darapladib). Darapladib has been shown to reduce LP-PLA2 and inflammatory markers and is currently being trialed to assess its effects on outcomes in ACS.[120]

The antitubulin agent colchicine lowers hs-CRP in patients with stable coronary artery disease[121] and has direct intracellular effects on the cells involved in atherosclerosis[122] and may be a low cost, widely applicable method of lowering CRP without the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs). A trial to assess the effect on coronary artery disease is currently underway.[123]

Even further upstream in the inflammatory cascade are the cell signaling transcription factors that trigger the release of proinflammatory cytokines and cell adhesion molecules. The most important of these is NFκB. Potential inhibitors of the NFκB pathways have been described,[124] including a number of naturally occurring substances.[125]

Plaque Stabilizing Potential of Interventions Used in Acute Coronary Syndromes (ACS)

Beta-Adrenergic Blockers

Beta-adrenergic blockers are widely used in acute coronary syndromes. While there is no evidence that the standard beta blockers exert their benefit on acute coronary syndromes through an effect on the unstable plaque or on endothelial function, a reduction in shear stress and flexion stress has been thought to be important.[126] A third-generation beta blocker, nebivolol, was shown to have some effects on in vitro markers of endothelial function,[127] but there is no firm data that this is of relevance to the management of the patient with an ACS. Of the more widely used beta adrenergic blockers, it has been shown that atenolol has no effect on endothelial-dependent forearm blood flow in hypertensive patients when compared to an ACE inhibitor,[128] nor was any effect on endothelial-dependent coronary vasomotion shown in patients with coronary disease.[129]

Calcium Channel Blockers

There is still uncertainty as to whether calcium channel blockers are effective or otherwise in acute coronary syndromes[130,131] and they are recommended only for symptom relief rather than for improving prognosis. There is no convincing evidence that any of the effects observed in clinical trials are due to an effect on plaque passivation or on endothelial dysfunction although the results with third-generation calcium channel blockers suggest a possible role.[132]

Organic Nitrates

Organic nitrates are commonly used in acute coronary syndromes. Their action is similar to those of nitric oxide, causing vasodilatation via an increase in intracellular concentrations of cyclic guanosine monophosphate, resulting in smooth muscle cell relaxation and antiplatelet effects.[133] Exogenously administered nitrates can act in the presence of a damaged endothelium. The effects of nitrates have been studied in acute myocardial infarction, but no convincing benefits have been shown in patients with unstable angina or non–ST-segment elevation.

Antioxidants

Since the production of reactive oxygen species (ROS) in the vascular wall has several deleterious effects, the potential for potent antioxidant therapies could be considered as a plaque-stabilizing strategy. A large number of epidemiologic observational studies have shown an association between atherosclerotic disease and low levels of antioxidant vitamins, but well-conducted studies have failed to show a clear benefit.[134] To date, there are no studies of the effect of antioxidant therapy administered in the early phases of acute coronary syndromes.

Estrogens

The effects of estrogens on the vascular wall are mediated by nongenomic and genomic mechanisms and any of these effects are potentially beneficial.[135,136] Despite that, there is clear evidence that estrogen therapy is unhelpful in the post coronary patient.[137] Obviously, further research is required to explain the discrepancy between the apparently beneficial biological effects of estrogen on the vascular wall and the adverse effects in clinical trials, and whether alternative methods of utilizing the effects of estrogen on the vascular

wall will deliver better clinical outcomes in acute coronary syndromes.

Blood Sugar Control

Disturbed endothelial function is well documented in diabetes.[138] The mechanisms by which diabetes affects endothelial function is not well understood, but advanced glycation end products, glycated and oxidized low-density lipoproteins and reactive oxygen species linked to hyperglycemia have all been implicated.[139] Intensive blood glucose control with sulfonylureas or insulin is associated with a reduction in microvascular, though not macrovascular, complications in type 2 diabetes,[140] and intensive control with metformin in overweight patients with type 2 diabetes is associated with reduced vascular endpoints.[141] The mechanism of this improvement over a 20-year follow-up period is not clear, but improved metabolic control in diabetic patients, whatever the treatment used, is associated with reversal of endothelial dysfunction.[142] The thiazolidinediones may exert specific effects on endothelial function by their ability to bind to peroxisome proliferator-activated receptors, which have been shown to be present in the vessel wall[143]; however, the safety of thiazolidinediones (glitazones) remains to be established.[144]

Smoking Cessation

There is some evidence that the deleterious effects of smoking are mediated by an effect on endothelial dysfunction.[145] This may also occur with passive smoking.[146] The effects in acute coronary syndromes have not been documented for obvious reasons, but the available data support the universal clinical recommendation that a patient with an acute coronary syndrome should immediately and permanently desist from smoking.

Dietary Intervention

There is evidence that dyslipidemia is associated with disturbed endothelial function.[147] High fat meals accompanied by postprandial rise in serum triglycerides can impair endothelial function within hours.[148] These effects were minimized when the high-fat meal contained antioxidant-rich foods.[149] Animal experiments have shown that hypercholesterolemic rabbits fed a low-fat diet show a reduction in cellular infiltrate and MMP activity and an increase in collagen accumulation in the fibrous cap compared with animals fed a high-fat diet.[150] This demonstrates a likely mechanism by which a low-fat diet can contribute to plaque stabilization in ACS. It has been hypothesized that the postprandial state can precipitate unstable coronary syndromes because of effects on the vascular wall leading to plaque instability.[151]

Inhibition of Neovascularization

Since the unstable atherosclerotic plaque is characterized by infiltration of vasa vasorum with the potential for rupture and leakage of inflammatory cells, the possibility of limiting neovascularization has been investigated.[152]

The Role of Percutaneous Coronary Intervention (PCI) in Plaque Passivation

The use of PCI in acute coronary syndromes is widespread, and the convincing results of recent trials of acute coronary intervention in acute coronary syndromes confirm the validity of this approach.[153] Until now, the target lesion for PCI in ACS patients has been the critical lesion, which is assumed to be the cause of the acute reduction in coronary blood flow. It is not clear if the benefits of coronary stenting in ACS are achieved by plaque stabilization or by other mechanisms. The use of PCI with drug eluting stents to treat plaques that are unstable but not critically obstructing the vessel is a potential future strategy for management of the patient with an ACS. There is no clinical trial data to support this approach, although serial angioscopic study shows that stenting can seal the unstable plaque by encouraging neointimal proliferation.[154]

Cyclooxygenase-2 (COX-2) Inhibitors and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Acute Coronary Syndromes

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors have potent anti-inflammatory effects and reduce hs-CRP and have even been suggested as potential candidates for stabilization of the unstable plaque.[155] However, reports that patients on COX-2 inhibitors have a higher risk of acute vascular thrombotic events[156] has led to the withdrawal of rofecoxib and caution in the use of celecoxib. There is evidence that the adverse effects of the COX-2 inhibitors may be due to an effect on endothelial function and enhancement of thrombosis by inhibiting the production of prostacyclin.[157] Recent reports indicate that the risks may be as high with all NSAIDs.[158,159] Until more observations become available, limited use of COX-2 inhibitors and NSAIDs in ACS is a sensible precaution.

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CHAPTER 27

Revascularization in Non–ST-Segment Elevation Acute Coronary Syndrome—For Whom, When, and How?

Lars Wallentin

The manifestations of ischemia in non–ST-elevation acute coronary syndrome (ACS), are caused by a severe flow-limiting stenosis or occlusion of a coronary artery. In the majority of cases there are also signs of myocardial infarction (MI), which might be related to thrombotic occlusion of the culprit coronary lesion as well as to downstream embolization of thrombotic material from the lesion. The thrombotic component of the disease can be influenced by treatment with platelet and coagulation inhibition.[1,2] Despite such treatment, most often there remains severe coronary stenoses leading to a risk of recurrences after the withdrawal of the initially intense antithrombotic treatment.[3-6] Therefore, there is a rationale for the early use of coronary angiography and revascularization. Elimination or bypassing of the flow-limiting lesions by coronary percutaneous intervention (PCI) or coronary artery bypass grafting (CABG) might be an appropriate complement to medication for rapid as well as long-term stabilization of the condition. The goal is that the early procedure also will contribute to a reduced risk of recurrences of severe angina and MI and thereby also contribute to the avoidance of development of heart failure and improved survival (Box 27-1).[7-11] Although early revascularization of a flow-limiting coronary lesion often seems an attractive way to solve the problem, still it needs to be emphasized that the treatment strategy needs to be based on the initial response and long-term outcome at the patient level.[11-13] Thus, the eventual benefits and risks are related not only to lesion characteristics but also to patient characteristics and their impact on the development of the disease and the risks for complications in association with invasive procedures.[14-16] Furthermore, health economy of the strategy needs to be consideraed: There needs to be an appropriate balance between the increased cost of the early procedures and their eventual compensation of avoiding readmission for recurrent events and late revascularization procedures.[17-19] The many issues influencing the decision making and recommendations in the selection between an early invasive and a primarily noninvasive treatment strategy in non–ST-elevation acute coronary syndrome are summarized in Box 27-1. Early invasive procedures are currently not the recommended strategy for all-comers with non–ST-elevation ACS but rather as a selective approach for moderate- to high-risk patients according to the latest international treatment guidelines.[1,2,20] Accordingly, in the non–ST-elevation population, currently early angiography is performed in about 65% to 90%, PCI in about 50% to 60%, and CABG in about 5% to 10% before discharge after the index event.[20-22] The basis for these recommendations is mainly the accumulated results from the large-scale prospective randomized trials comparing an early routine versus a selective ischemia-based invasive treatment approach.[7-13,23,24] The short- and long-term results from these trials will also be the main basis for the current review on for whom, when, and how early revascularization procedures should be performed in non–ST-elevation ACS (Fig. 27-1).

FOR WHOM?

Evidence for the Benefit of an Early Invasive Strategy

Three large scale prospective randomized trials (FRISC-2, TACTICS-TIMI-18, and RITA-3)[7-13] have compared an early routine invasive strategy versus an ischemia-driven conservative strategy with an adequate separation in proportion of early procedures between the two arms in the studies (Fig. 27-2). These were the first three trials where all patients also received most of the currently recommended intense antithrombotic medication and had the majority of revascularization procedures either as PCI with routine stenting or CABG (Table 27-1). All three trials demonstrated the superiority of an early invasive strategy compared with a primarily noninvasive one concerning the composite of death, MI, and recurrent severe angina. Although there was an early hazard with more procedure-related MIs and deaths in association with the procedures while in hospital,[25] in the first two

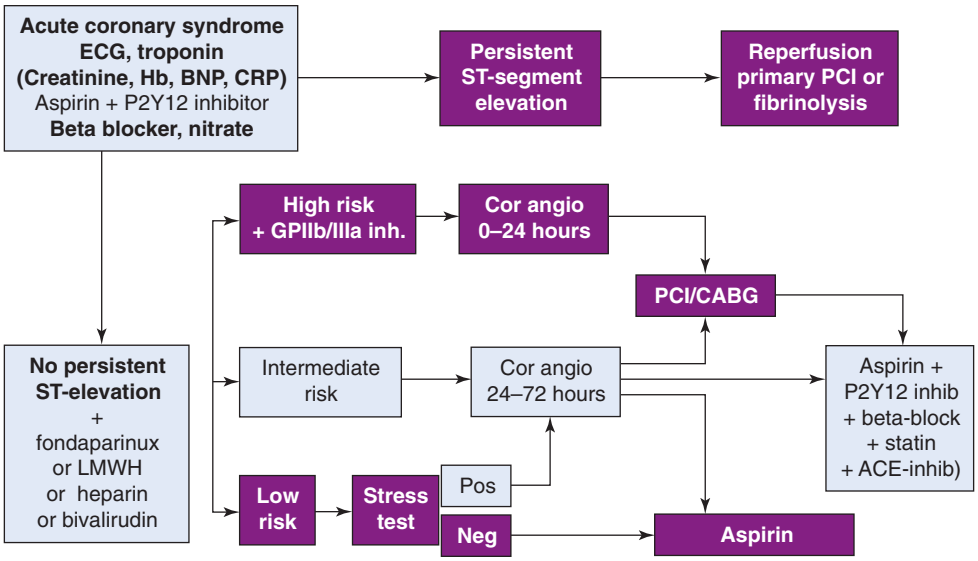


FIGURE 27–1 Overview of recommended treatment strategy in acute coronary syndrome.

studies (FRISC-2, TACTICS-TIMI-18) there was a reduction in the composite of death and MI already at 6 months.[10,11] In the two trials with long-term follow-up to 5 years there was also a maintained reduction in the composite of death and MI and a trend to improved overall survival (Fig. 27-3A-C).[7,13] Also in meta-analyses[2,25-27] there is a support for the overall superiority of the early invasive regimen also when taking into account the more equivocal results of the older TIMI-IIIB,[28] VANQWISH,[29] and smaller MATE,[30] VINO,[31] ISAR-COOL[32] and the latest ICTUS[23,24] trials. In the latest performed ICTUS trial there appeared, surprisingly, no advantages when comparing an early invasive approach in all comers with troponin-elevation on admission for non–ST-elevation ACS versus a more selective approach with early revascularization in those with signs of ischemia at rest or exercise (Fig. 27-3D).[23,24] However, the differing outcome in this trial might mainly be explained by a substantial early crossover of 44% of the noninvasive patients to an invasive regimen (see Table 27-1, Figs. 27-5 and 27-6), and also of an eventual exclusion of the higher risk population sent to early invasive procedures based on the results from the previous trials already available at the start of the ICTUS trial. Much of the difference in outcome between these trials might be explained by the different management finally used in the different arms, as in some trials patients in the invasive arm had less than 50% early revascularization procedures and/or a 35% to 45% early revascularization rate also in the noninvasive arm (see Table 27-1, Figs. 27-5 and 27-6). Therefore it is not surprising that the overall results in a meta-analysis including all these heterogeneous trials only show a modest 16% relative reduction in the composite of death and MI after one year.[2] Only in the study with the largest contrast, 62% in-hospital difference in revascularization procedures, there was a significant improvement in survival by the early invasive approach.[7-9] Furthermore there was, especially in the trials with a larger contrast in procedure rates between the treatment arms, a substantial reduction in anginal symptoms,[8-13,33] exercise tolerance and exercise induced ischemia,[34] readmissions to hospital,[8-13] and an improved quality of life.[35-37] The most relevant estimate of the effects of an early invasive versus selective invasive treatment strategy in a contemporary treatment environment might be obtained by including only the seven trials that exclusively randomized patients with a diagnosis of non–ST-elevation ACS and where the currently recommended treatments of thienopyridine and glycoprotein (GP) IIb/IIIa and coronary stents were available for use during PCI. Using such an approach there appeared at 2-year follow-up significant relative reduction of 25% in mortality, 17% in nonfatal reinfarction, and 31% in recurrent unstable angina (Fig. 27-4A-C).[27]

BOX 27-1 Issues Influencing the Decision Making and Recommendations in the Selection of an Early Invasive Versus a Primarily Non-Invasive Treatment Strategy in Non–ST-Elevation Acute Coronary Syndrome

Benefits
Survival
Recurrent myocardial infarction
Late revascularization
Late readmission
Recurrent incapacitating angina
Need for anti-anginal medication
Quality of life

Risks
Procedure-related mortality
Procedure-related myocardial infarction
Procedure-related extra-cardiac side effects and morbidity
Restenosis and recurring need for revascularization
Recurrence of angina

Costs
Procedure-related costs
Length of hospital stay
Costs of medication
Costs for sick-leave and retirement pension
Patient selection
Risk indicators and risk scores in relation to benefit, risks, and cost
Optimal revascularization method
Optimal timing of revascularization

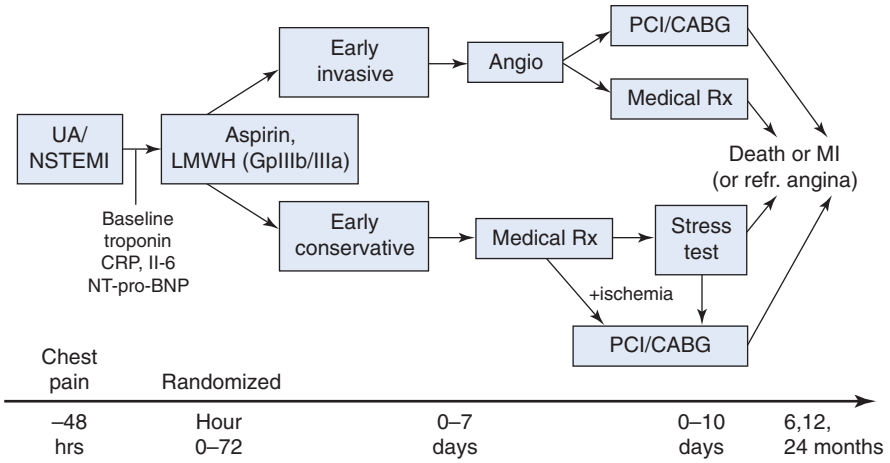


FIGURE 27–2 Overview of the design of the four large prospective randomized clinical trials (FRISC2, TACTICS-TIMI-18, RITA-3, ICTUS) on an invasive versus a noninvasive strategy in non–ST-segment elevation acute coronary syndrome. UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction.

TABLE 27–1 Early Invasive Strategy Versus Early Noninvasive Strategy in Unstable Coronary Artery Disease*

	FRISC II[10]		TACTICS[11]		RITA3[12]		ICTUS[23]	
N	2457		2220		1810		1200	
Time period	1996-1998		1997-1999		1997-2001		2001-2003	
Baseline findings on admission								
Inclusion diagnosis	NSTEMI/UA		NSTEMI/UA		UA		NSTEMI	
Median age	65		62		62		62	
Female %	31		34		38		27	
Diabetes mellitus	12		28		13		13	
Previous MI	22		39		28		23	
ST-segment depression	46		39		37		48	
Biochemical marker elevation	57		37		18		82	
	Ninv	Inv	Ninv	Inv	Ninv	Inv	Ninv	Inv
Angiography								
Before discharge—7 days %	10	96	51	97	16	96	53	98
6-12 months %	47	98	61	98	48	97	67	99
Extent of CAD (invasive group)								
0 v.d. %	—	14	—	13	—	22	—	—
1 v.d. %	—	30	—	—	—	33	—	—
2 v.d. %	—	26	—	—	—	24	—	—
3 v.d., LMD %	—	31	—	43	—	22	—	—
Revascularization								
Before discharge.—10 days %	9	71	36	60	10	44	40	76
Within 6-12 months %	43	78	44	61	28	57	54	79
CABG 6-12 months %	23	37	16	22	12	21	14	18
PCI 6-12 months %	20	41	28	40	16	36	40	61
Non-revasc. with 1-3 v.d. 10 days, %	—	15	—	27	—	34	—	—
Non-revasc. with 1-3 v.d. 12 months, %	—	8	—	26	—	21	—	—
Outcome 6-12 months								
Death or MI or severe angina %	42.2	13.2	19.4	15.9	14.5	9.6	21.2	22.7
Death or MI in all patients %	14.1	10.4	9.5	7.3	8.3	7.6	—	—
Death or MI in men %	15.8	9.6	—	—	10.1	7.0	—	—
Death or MI in women %	10.5	12.4	—	—	5.1	8.6	—	—
Death %	3.9	2.2	3.5	3.3	3.9	4.6	2.5	2.5
Spontaneous MI %	11.3	4.2	—	—	5.7	3.3	4.6	3.7
Procedure related MI %	2.1	5.4	—	—	0.4	1.7	5.4	11.3

*Overview of four large randomised trials including more than 1000 patients and were performed over 7 years using baseline treatment with aspirin, heparin, or LMWH and with availability of glycoprotein IIb/IIIa inhibitors and stents followed by thienopyridine.

UA, unstable angina; NSTEMI, non ST-segment elevation myocardial infarction; v.d, coronary vessel disease; LMD, left main coronary artery disease; Ninv, noninvasive; Inv, invasive.

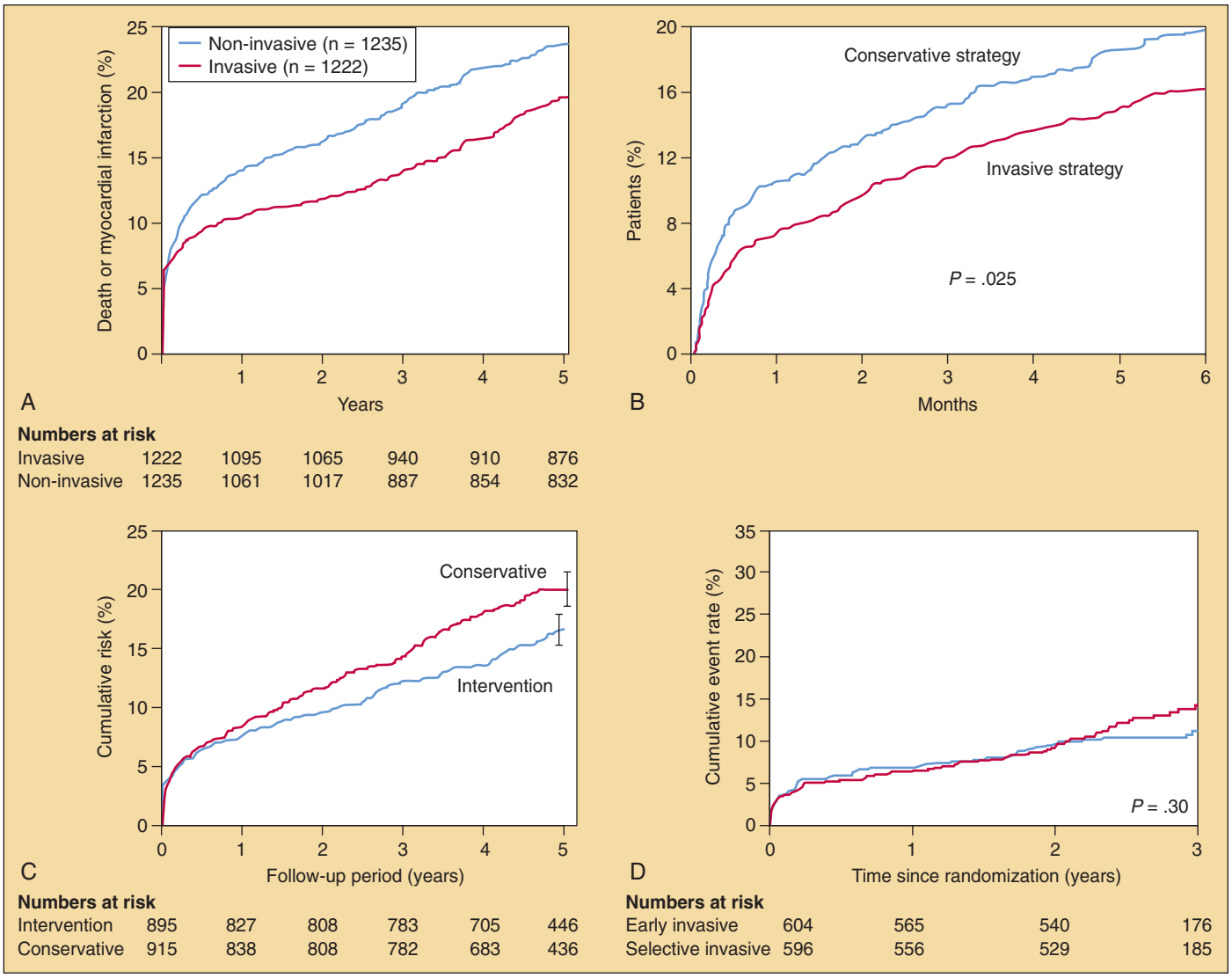
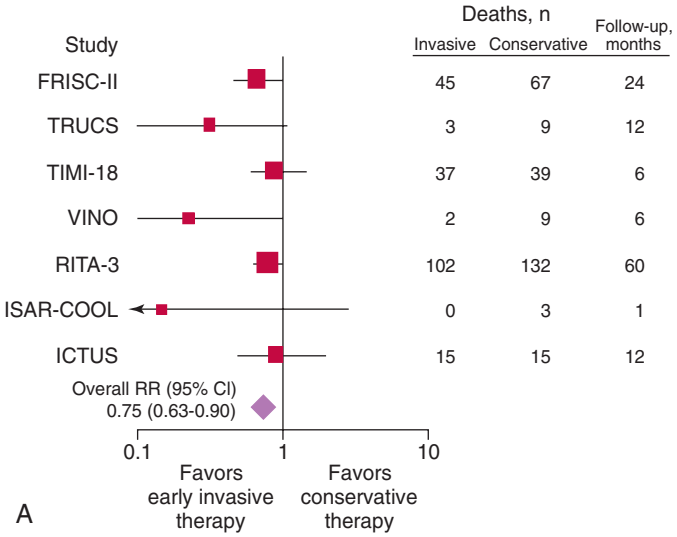
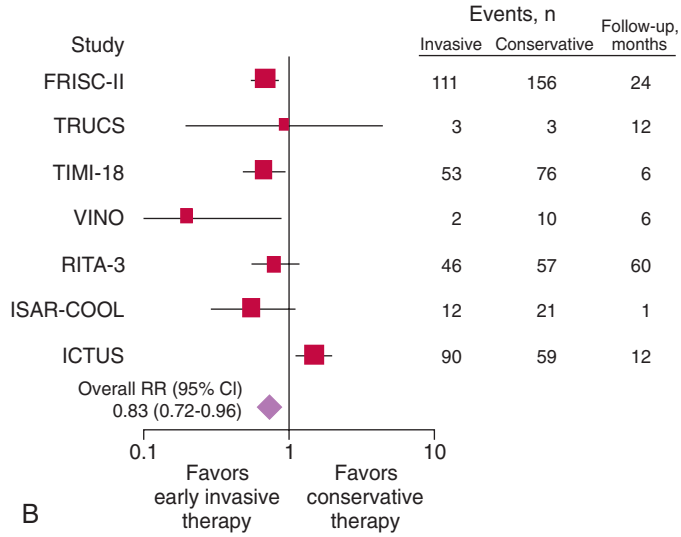


FIGURE 27–3 Longest term outcome of the four large prospective randomized trials in non–ST-segment elevation acute coronary syndrome. **A**, Five-year outcome of the primary endpoint—death or myocardial infarction—in the FRISC 2 trial. **B**, Six-month outcome of the primary endpoint—death, myocardial infarction and rehospitalization for acute coronary syndrome—the TACTICS-TIMI 18 trial. **C**, Average 5 year outcome of the composite endpoint of death, myocardial infarction in the RITA-3 trial. **D**, Average 3 year outcome of the composite endpoint of death and spontaneous myocardial infarction in the ICTUS trial. (***A**, From Lagerqvist B, Husted S, Kontny F, et al: 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: A follow-up study. Lancet 2006;368:998-1004. **B**, From Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-1887. **C**, From Fox KA, Poole-Wilson P, Clayton TC, et al: 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: The British Heart Foundation RITA 3 randomised trial. Lancet 2005;366:914-920. **D**, From Hirsch A, Windhausen F, Tijssen JG, et al: Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): A follow-up study. Lancet 2007;369:827-835.)*

Cost Effectiveness

Several health economy analyses have demonstrated that the higher initial costs for an early invasive strategy might be partly compensated for by lower costs during longer-term follow-up for length of hospital stay, rehospitalizations, late procedures, outpatient visits, and medical treatment. In the 1-year perspective a strategy of routine catheterization and, if appropriate, revascularization, was, in the FRISC-2 study, associated with higher costs than a strategy of invasive procedures only with severe ischemia or recurrent MI.[17,18] However, the costs of the invasive strategy can be reduced by performing invasive procedures earlier, within the first 48 hours, as such an approach results in shorter hospital stay.[38] Using such a strategy in the routine early catheterization arm, and comparing to a nonroutine catheterization strategy with wider indications for early revascularization based on non-invasive risk indicators, there were small differences in costs between these two strategies in the TACTICS trial (Fig. 27-7).[19] Thus, in a setting where revascularization is needed





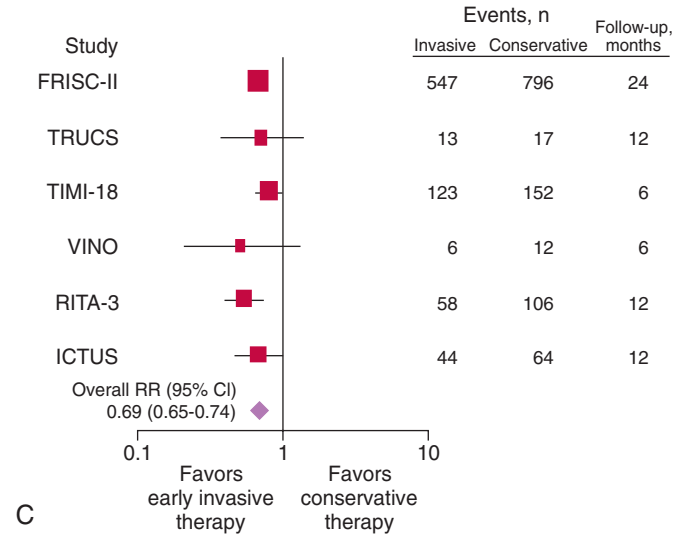


FIGURE 27–4 **A**, Meta-analysis showing the relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. **B**, Meta-analysis showing the relative risk of non-fatal myocardial infarction for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. **C**, Meta-analysis showing the relative risk of recurrent unstable angina requiring rehospitalization for early invasive therapy compared with conservative therapy at a mean follow-up of 13 months. *(From Bavry AA, Kumbhani DJ, Rassi AN, et al: Benefit of early invasive therapy in acute coronary syndromes: A meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006;48:1319-1325.)*

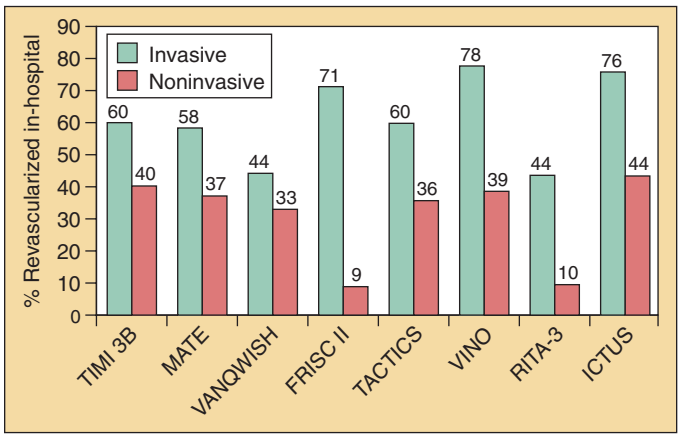


FIGURE 27–5 Proportion revascularized in hospital in prospective randomized trials of an early invasive compared to a noninvasive approach in non–ST-segment elevation acute coronary syndrome.

in 40% to 50% of the patients within the next year, as seen both in the FRISC-2 and TACTICS trials, there is only a modest increase in cost, provided that the early routine invasive procedures are performed within the first 48 hours after admission. Therefore, an early invasive strategy might, in the longer term perspective, be cost-effective if the invasive procedures are performed without undue delay. This approach will also be preferred by the patients because the initial hospital stay is shortened and readmissions for recurrent symptoms avoided. Thus, compared with a primarily noninvasive approach, an early invasive strategy in ACS is associated with a trend toward improved late survival, lower morbidity, and improved quality of life at a modest increase in cost for the health care system. These beneficial results in the prospective randomized trials are also supported by similar experiences in adjusted comparisons between patients managed with an early invasive versus a conservative approach in some real life registries or pharmaceutical clinical trials.[39-41]

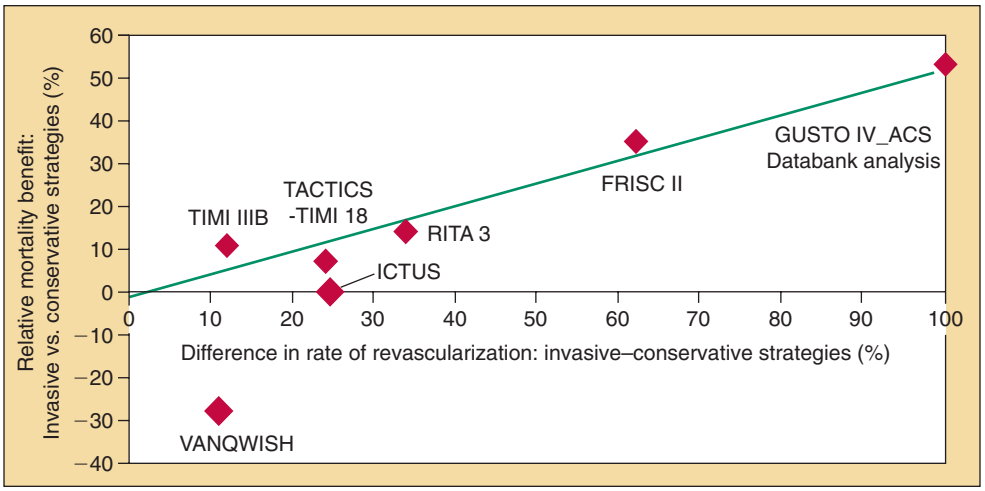


FIGURE 27–6 The ability to demonstrate relative mortality benefit with the revascularization strategy depends on the gradient in rates of revascularization between both randomization arms. *(From Bassand JP, Hamm CW, Ardissino D, et al: Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-1660.)*

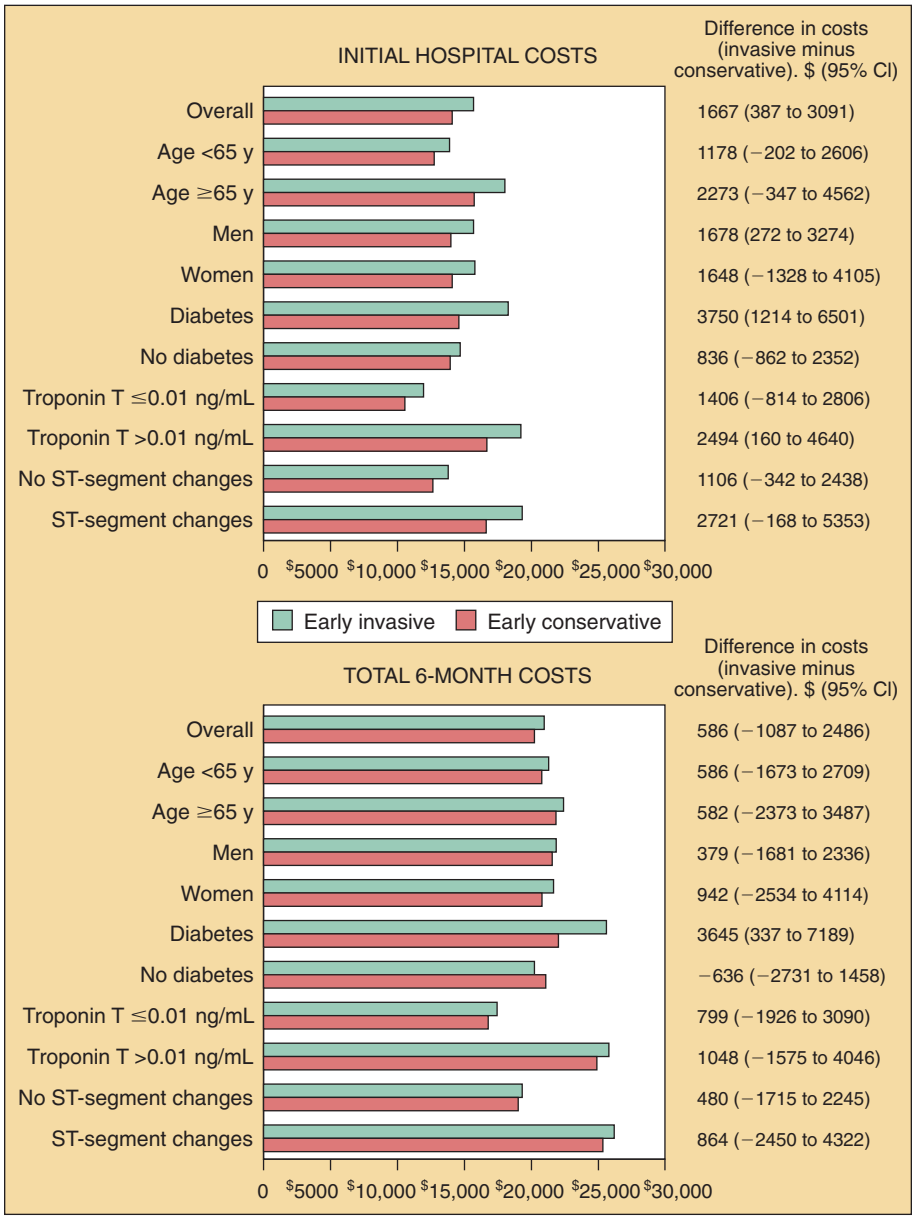


FIGURE 27–7 Initial hospitalization and 6-month costs in the total material and different subgroups in the TACTICS-TIMI-18 trials. *(From Mahoney EM, Jurkovitz CT, Chu H, et al: Cost and cost-effectiveness of an early invasive vs. conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. JAMA 2002;288:1851-1858.)*

BOX 27-2 Risk Indicators to Use for Selection of Patients for Early Invasive Treatment in Acute Coronary Syndrome

Age (>65 years)
Coronary risk factors—diabetes mellitus, hyperlipidemia, hypertension, smoking
Renal dysfunction (glomerular filtration rate [GFR] <90 mL/min, even higher at <60 mL/min and highest at <30 mL/min)
Previous myocardial infarction, previous angina pectoris
Cardiac dysfunction—elevated NT-proBNP (>300 ng/L, even higher risk at >1000 ng/L)
History of chest pain at rest, or during last 24 hours, or recurrences despite treatment
Myocardial ischemia—ST-segment depression (≥0.1 mV, even higher risk at ≥0.2 mV)
Coronary thrombosis—elevated troponin (troponin T ≥0.01, even higher risk at ≥0.5 µg/L)
Inflammation—elevation of C-reactive protein (>10 mg/L)
Severe coronary artery lesion at coronary angiography

Risk Stratification for Selection of Patients for Early Invasive Procedures

As with most other treatments, the risk reduction by an early invasive treatment is larger in patients at higher risk, and symptom relief better in patients with more severe symptoms. Many clinical and laboratory observations are related to the subsequent risk of new events after ACS as summarized in Box 27-2 and presented in previous chapters. Thus, much prognostic information is already available in the patients' history; that is, the risk is raised by age, male gender, diabetes mellitus, chronic kidney disease, previous MI, previous severe angina, congestive heart failure, or medication for any of these conditions.[14-16,42,43] The severity of the manifestations of the disease (e.g., episodes of chest pain during the last 12 to 24 hours and/or recurrent episodes of pain despite pharmacologic treatment) is associated with higher risk.[44,45] Signs of ischemia (ST-segment depression) in an electrocardiograph (ECG) at entry and/or episodes of ST-depression during continuous monitoring are also related to a worse prognosis.[46-57] Left ventricular dysfunction, as evaluated by elevation of N-terminal prohormone brain natriuretic peptide (NT-proBNP) test or echocardiography, are other observations associated with guarded prognosis.[39,58-64] Recently also a moderate renal dysfunction (e.g., glomerular filtration rate (GFR) of less than 90 mL/min,[16,61,65-71] or an elevated cystatin-C level[72]) have been found associated with worse outcome. The occurrence of elevated biochemical markers of MI, i.e., troponins, is a well established marker of raised risk for subsequent MI as well as mortality.[45,54,61,73-85] Recently, biochemical markers of inflammatory activity (e.g., C-reactive protein (CRP)[14,60,61,83,86-93] and interleukin-6,[94-97] platelet activity [i.e., CD40-ligand],[98-100] and of cellular stress and repair [i.e., GDF15][101,102]) have been shown associated with a worse prognosis. The combination of several of these risk indicators provides a better risk stratification than any marker alone. Thus, the combination of ST-segment depression as a probable indicator of severe coronary stenosis, elevation of troponin as a marker of coronary thrombosis and/or MI, elevation of NT-proBNP as a marker of reduced cardiac performance, reduced creatinine clearance as an indicator of renal dysfunction, elevated CRP as an indicator of inflammatory activity, and elevation of GDF15 as a marker of cellular stress provide better prognostic information than any of these alone. The multivariate analyses of the combination of the patient history, clinical presentation, and several of these laboratory markers have allowed the development of risk scores of key factors containing the most important prognostic information.[14-16,42] As most of these variables are easily and rapidly available within a short time after admission, they can also be widely applied as a support for the selection of patients for early invasive treatment in clinical practice (Fig. 27-8).

Risk Stratification in Relation to the Effects of Invasive Treatment

The two largest trials randomizing patients to an early invasive versus a selected invasive strategy, FRISC-2 and TACTICS-TIMI-18, have provided a wealth of information on the outcome of an invasive strategy in relation to risk stratification while only limited information is available from the other trials (RITA-3, ICTUS).[13] Therefore the present chapter will mainly use the results from the first two trials as a basis for the currently most appropriate indications for early revascularization.

Both the FRISC-2 and the TACTICS-TIMI-18 trials showed that the absolute risk reduction concerning subsequent coronary events was larger in patients at higher risk according to most of these risk indicators (see Fig. 27-8.)[7,11,14] The invasive treatment was associated with a larger risk in older patients. Still, there was larger relative as well as absolute benefit in patients older than 65 years of age.[7,103] Corresponding findings have also been reported from observational trials.[41,104] However, the real life experiences show that early revascularization procedures are less often used in the elderly.[105-108] Likewise, patients with diabetes mellitus have a considerable increased risk for ACS.[14,43,109-112] However, the proportional risk reduction by early revascularization was similar in patients with and without diabetes. Accordingly, the absolute risk reduction in death and MI was larger in patients with diabetes.[43,110] Despite these successful results, there is an underutilization of early revascularization procedures in patients with diabetes.[109,113] Also patients with left ventricular dysfunction[60] or renal dysfunction[114] were at higher risk but still they had similar relative and thereby a larger absolute risk reduction by the early invasive approach. Patients with signs of severe ischemia as indicated by the degree of ST-segment depression or T-wave changes in ECG at rest had a considerably larger benefit from early invasive procedures than patients without these findings.[46,48,115] Both the FRISC-2 and the TACTICS trials indicated that the majority of patients benefiting from an invasive strategy were found in patients with detectable troponin in serum samples at entry.[11,47,60,84,85] The risk of a subsequent infarction was similar in all patients with any elevation of troponin while there was a linear relation between the level of troponin and mortality.[81,83] Thus, in the prioritization of patients for invasive procedures any detectable troponin would suggest an invasive approach, while the urgency of the procedure is raised at higher troponin levels. Patients without any detectable troponin are at very low risk and have little to gain from invasive procedures unless indicated by incapacitating symptoms of angina or the presence of other clinical or biochemical risk indicators.[11,47] In relation to the levels of C-reactive protein the relative effects of the invasive approach were similar at all levels and, thereby, the absolute effects are larger in patients with higher levels of these inflammation markers.[60] However, according to the FRISC-2 study results, the initial level of interleukin-6 seemed to be a more specific marker both of raised mortality and the effects of the early invasive treatment.[96] Recently also the presence of elevation of GDF15 has been shown to be an independent indicator of a larger benefit of an early invasive approach in non–ST-elevation ACS.[101] Therefore in the future, a combination of clinical history, signs of ischemia at ECG, and a combination

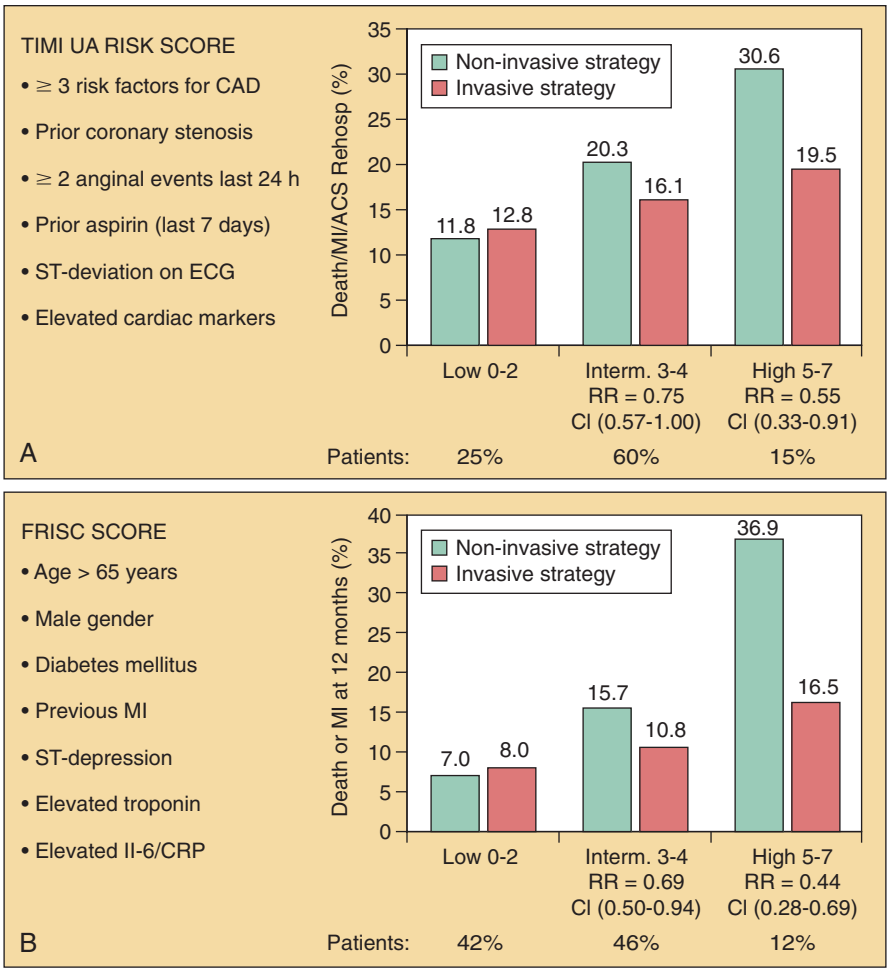


FIGURE 27–8 **A**, Outcome of an early invasive strategy in relation to the TIMI UA risk score in the TIMI-18/TACTICS trial. **B**, Outcome of an early invasive strategy in relation to the FRISC-2 score in the FRISC-2 trial. (***A,*** *From Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-1887.* ***B,*** *From Lagerqvist B, et al: FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. Heart 2005;91:1047-1052.)*

of biochemical markers such as troponin, creatinine clearance, NT-pro-BNP, and GDF15 might provide the best information on the indication for an early invasive treatment strategy in non–ST-elevation ACS.[101,116]

Risk Scores in Relation to the Effects of Early Invasive Treatment

Using combinations of several markers both the FRISC-2 and the TACTICS-TIMI-18 trial demonstrated that the benefits of the invasive strategy seemed confined to patients with a combination of elevated troponin level and ST-segment depression. However, the outcome based on troponin and ST-segment depression was modulated by the other factors such as age, diabetes, renal dysfunction (creatinine clearance), previous MI, left ventricular dysfunction (NT-proBNP), severity of previous and current symptoms of angina, cellular stress (GDF15) and inflammatory activity (CRP, IL6). Using a multivariable approach, it is possible to identify the minimal set of key risk factors needed as components of a risk score for evaluation of prognosis and selection of invasive treatment.[11,14] According to these risk scores, the largest benefit of an early invasive treatment was seen at higher scores, that is, in patients with several of the risk indicators (see Fig. 27-8). Patients with a high risk score (≥5 risk indicators) had improved survival as well as a lower risk of (re)infarction. At an intermediate risk score (3-4 risk indicators) there was mainly a reduction in (re)infarction. Finally the early invasive treatment, with its inherent risk for peri-procedural complications, did not reduce the risk of death or MI in the low risk score patients (0-2 risk indicators). However, it needs to be emphasized that low-risk as well as high-risk patients with incapacitating symptoms obtain the same symptom relief and improvement in quality of life from the invasive procedures.[8-13,20,33,35] Thus, in many cases there might, because of symptoms, be reasons to consider invasive procedures even in lower-risk patients. However, the urgency of the procedures is less in such patients because of their lower risk for coronary events while awaiting the procedures. Finally, it needs to be emphasized that all these risk scores have been derived from retrospective analyses and, so far, no risk score has been verified in a prospective randomized trial.

Stress Tests for Risk Stratification

In low-risk patients, a stress test will allow further risk stratification. At these tests a new high-risk category is constituted by either large or multiple areas of exercise-induced myocardial ischemia or low exercise tolerance.[117-124] A low risk category is defined by an adequate exercise tolerance without any signs of ischemia. In the high-risk category early catheterization and revascularization is indicated. In the low-risk category no early invasive procedures should be performed,

as the peri-procedural risks are greater than the potential benefits that can be obtained in this patient category.[125-127] In the ICTUS trial a strategy with a stepwise decision making with an initial decision for invasive procedures based on clinical presentation and signs of ischemia at rest followed by a second decision for invasive procedures at ischemia at a pre-discharge exercise test was found to provide similar long-term outcome as a direct invasive approach in a troponin positive patient population recruited in centers with an overall high rate of early invasive procedures.[24]

Coronary Angiography for Early Risk Stratification and Selection of Treatment

In many instances the performance of coronary angiography might provide the most reliable information concerning risk stratification and selection of treatment for an individual patient. Not only the culprit lesion and its characteristics are identified but also the extent of coronary artery disease, the existence of collaterals, the myocardial area at risk, and the left ventricular function are elucidated by the catheterization.[128] In patients with a clinical diagnosis of ACS there is about 10% with disease of the left main artery, 25% with three-vessel disease, 25% with two-vessel disease, 25% with one-vessel disease and 15% with no significant coronary artery disease at coronary angiography (see Table 27-1). Most of the above outlined risk indicators, i.e., age, male gender, diabetes, previous MI, previous severe angina, renal dysfunction, left ventricular dysfunction (elevated NT-proBNP), ST-segment depression, elevated troponin, elevated GDF15, and higher risk response at a stress test, are associated with a raised occurrence of multivessel- or left main coronary artery disease.[46,81,119,120,129-133] However, the correlation between these risk indicators and the extent of coronary artery disease are rather weak. Thus, from the individual patient's perspective it might be preferable to use the combined results from a coronary angiography and from the noninvasive risk indicators as a basis for a decision of early revascularization. The possible disadvantage of such an approach is that all lesions identified at coronary angiography tend to be dilated and stented at the same session, disregarding the eventual information from other risk indicators. In the invasive arm of the FRISC-2 trial there was no relation between the extent of initial coronary artery disease and subsequent coronary events in the invasive arm, indicating that the early invasive procedures will eliminate the risk for new events associated with severe coronary lesions. These findings support the recommendation of early coronary angiography in the majority of ACS patients in order to identify all severe coronary lesions, the risk of which can be reduced by early revascularization.

Gender and Selection of Invasive Treatment

In the FRISC-2 and the RITA-3 trials there was a significantly better effect of the invasive strategy in men than in women.[134,135] This might partly be explained by the lower proportion of women revascularized in the invasive group because of the lower rate of significant lesions in females than males. Another reason might be a raised risk for peri-procedural complications, especially with diabetes mellitus and higher age, in the women with coronary artery bypass surgery.[134,135] However, these gender-related differences in the effects of early invasive treatment were observed in neither the TACTICS-TIMI-18[136] nor the ICTUS trial[23] nor in reports from observational materials.[41,137] In a meta-analysis of all published prospective randomized trials there appeared no significant difference between genders in the overall benefit concerning the composite of death, MI and recurrence of severe angina.[138] In women as well as in men the benefits were confined to those at higher risk, that is, with elevated troponin and/or ST-depression in the ECG at rest. In order to properly evaluate women with ACS it seems preferable to use the same indications for diagnostic coronary angiography in both genders, that is, at moderate to high risk of subsequent events according to the risk stratification criteria discussed earlier. However, in the selection of the most appropriate treatment, the better long-term prognosis and the higher peri-procedural risks in women compared to men should be taken into consideration. Finally, because of the uncertainties of the balance between benefits and risks in women new prospective trials comparing an early invasive versus a conservative strategy focusing on women are warranted.

Special Situations

Chronic kidney disease has over the last several years appeared as a very important indicator of raised risk of future events in ACS.[16,61,65-72] Several studies have shown that chronic kidney disease is associated with a more severe atherosclerotic disease, increasing the risk of future events.[70,139,140] Additionally, chronic kidney disease also raises the risk of complications for many kinds of medical treatment because of the risk of overdosing at slow rates of excretion. Accordingly chronic kidney disease is a well established risk factor for bleeding both at anticoagulant and antiplatelet treatment both of which are used abundantly in ACS.[68,141] The administration of contrast agents at coronary angiograms and PCI procedures also carries a risk of at least temporary impairment of kidney function.[142] Such temporary deterioration of kidney function might be associated with risks of appearance of side effects to previously well accepted medications. Finally chronic kidney disease also carries an increased risk for the need of surgical procedures such as CABG. Despite increased risks of side effects, both individual trials[114,143] and meta-analyses[144] indicate that patients with reduced renal function derive the same benefit from early invasive procedures as patients at moderate to high risk based on other risk indicators. Therefore there is little reason not to proceed to early invasive procedures because of reduced creatinine clearance which rather should strengthen the indication unless there are other contraindications.

WHEN?

In non–ST-elevation ACS, the risk for new events is highest during the first hours and days and tapers over the first 2 to 3 months. In non-revascularized patients, 40% of new events occur during the first 2 weeks, another 40% until 6 months, and 20% during the second half-year. Thus, treatment measures that aim for protection against new events need to be performed as early as possible. Accordingly patients with suspected or definite ACS should immediately on admission, if not started earlier, receive combination treatment with platelet inhibition by aspirin, P2Y12 receptor-inhibition and anticoagulation by unfractionated or low-molecular-weight heparin (LMWH), fondaparinux, or bivalirudin.[1,2] The risk stratification process, based on history, clinical presentation, response to treatment, ECG-findings and biochemical markers, should also start on admission and the identification of high risk patients to be concluded within the first few hours.[1,2] In patients at high risk, and especially those with clinically apparent persistent or recurrent symptoms or signs of ischemia, arrhythmia or hemodynamic compromise, the antithrombotic treatment should be intensified, usually by the addition of GP IIb/IIIa inhibition by abciximab, eptifibatide or tirofiban,[11,145-148] and the patient taken immediately to the catheterization laboratory for invasive procedures (see Fig. 27-1).

In patients where the symptoms and signs of ischemia have subsided, but who still remain at high risk because of other risk indicators, the diagnostic coronary angiography and associated catheter-based interventions can also be performed immediately without undue risk, using this pharmacologic approach.[149] In high-risk patients invasive procedures are recommended within the first 24 hours rather than later during hospital stay, as such an aggressive strategy reduces the risk of recurrent ischemia, reinfarction, stroke and death, as compared with later interventions. The data on the advantages of very early interventions are consistent based on the reported outcomes in the TIMACS trial randomizing 3031 patients to an early versus a delayed invasive strategy,[150] and the observations that earlier procedures seem to protect the patient from ischemic events while waiting for procedures in older trials.[32,151,152] In patients at intermediate risk, the diagnostic catheterization and eventual revascularization procedure might safely be delayed for a few days under the protection of continued intense anti-thrombotic treatment. In these patients the long-term gains by an invasive strategy might not compensate the inherent hazards in an immediate revascularization procedure as seen in several of the randomized studies.[7,11,23]

In high-risk patients who cannot be adequately revascularized by angioplasty, the combination treatment with aspirin, parenteral anticoagulation and a GP IIb/IIIa inhibitor with short half-life should be continued until the time of coronary bypass surgery.[153] If thienopyridine-treated patients are clinically stabilized, it is recommended to postpone the surgical procedure for 5 to 7 days after cessation of this treatment to avoid the raised risk of bleeding complications.[154,155] A few days of stabilization of the coronary lesion and recovery from myocardial ischemia before proceeding to the CABG procedure have previously been considered advantageous for the overall outcome of surgery as it was associated with a very low rate of complications and mortality in surgically treated patients in the FRISC-2 trial.[10] However, there is a delicate balance between the gains obtained by reduction in time-to-treatment and the risks of bleeding and other peri-procedural complications that needs to be taken into account when deciding the optimal timing of catheter-based and surgical revascularization procedures.

Finally, in patients without remaining or previous symptoms of ischemia, and who are in the low risk category, further diagnostic procedures with stress testing are needed as the risk of peri-procedural complications might outweigh the potential benefits of invasive procedures concerning recurring ischemic events. Using such a risk-stratification–based approach will optimize the utilization and timing of invasive procedures to the benefit both of the patient and cost-effectiveness of the health care system.

HOW?

How to perform the revascularization procedures will depend on the extent and severity of the coronary lesions as well as patient characteristics such as age, gender, renal function, concomitant diseases and medications. The coronary angiogram contains the decisive information concerning suitability for PCI or CABG. In patients with non–ST-elevation ACS significant epicardial coronary stenosis will be present in about 30% in one vessel, about 30% in two vessels and about 30% in three vessels or the left main coronary artery (see Table 27-1). The rate of patients with no significant coronary lesion is about 10%. However, this proportion is higher in women with about 20% to 30% as compared with men, at 5% to 10%. Accordingly, in women there are lower proportions of patients with multivessel (two or three vessel) disease as compared with men.[134] Most prospective randomized trials have aimed for "complete" revascularization of all identified significant coronary lesions both at early and later interventions. Still it is important to try to identify the culprit lesion even at multi-vessel disease in order to make it a primary target for revascularization. In most cases the culprit will be possible to identify by combining information on lesion characteristics (eccentricity, irregularity, ulceration, haziness and filling defects) and localization of myocardial ischemia based on ECG findings and wall motion abnormalities.[156]

After the performance of the early prospective randomized trials (FRISC-2, TIMI-18, RITA-3) the results of PCI in non–ST-elevation ACS has been further improved with the expanded use of drug eluting stents and the combination with more intense platelet inhibition,[157,158] and also more intense treatment with statins and angiotensin-converting enzyme (ACE) inhibition as used in the ICTUS trial. The risk of bleeding complications at interventions might currently be attenuated by the use of the newer anticoagulant agents, including bivalirudin or fondaparinux, instead of unfractionated or LMWH.[159,160] In patients with a raised risk of bleeding because of oral anticoagulation, high age, female gender, low body weight or renal dysfunction, the use of the radial approach has also become a commonly used alternative to reduce the bleeding risk (unless intra-aortic balloon counterpulsation is foreseen).[161] Furthermore, the risk of early and late abrupt closure and stent thrombosis has, during recent years, been reduced by more intense treatment with dual platelet inhibition combining aspirin with P2Y12 inhibition with higher loading doses, starting earlier before procedures and maintaining it for at least 1 year.[155,162-166]

The rates of in-stent restenosis have been reduced by the common use of drug eluting stents (DES) also in the non–ST-elevation patient population. Although the efficacy and safety of DES have not been prospectively tested in non–ST-elevation ACS, these devices appear to have the same results in this setting as shown from subgroup analyses of several randomized trials and registries.[167] Although the incidence of stent thrombosis is higher after urgent procedures in non–ST-elevation ACS as compared with elective procedures in stable patients, there is no differences whether DES or bare metal stents (BMS) are used.[155] However, BMS should be preferred in settings where dual antiplatelet treatment might be interrupted (e.g., because of need for oral anticoagulation or surgery). In order to minimize the risk of stent thrombosis it is currently recommended that dual antiplatelet therapy should be maintained for at least 1 year after non–ST-elevation ACS and especially after implantation of DES. Currently there is no definite evidence for any differences in survival or risk for stent thrombosis or reinfarction between BMS or DES in non–ST-elevation ACS.[167-171] Therefore, the selection between these devices should be based on an individual assessment of benefit versus potential risk, and cost.[172]

The main problem with evaluation of the benefit of PCI in non–ST-elevation ACS is the remaining frequent occurrence of peri-procedural elevation of biomarkers, that often fulfill the criteria for MI. In the new guidelines for diagnosis of MI these procedure-related events will be referred to a special subcategory, separate from spontaneous events, which might facilitate more appropriate comparison of events in future trials.[173] The results of the current trials clearly show that early invasive procedures substantially reduce subsequent spontaneous MI, but at the cost of early in-hospital, often clinically silent, episodes of myocardial damage in association with the procedures.

Over recent years, the proportion of patients with non–ST-elevation ACS that have early revascularization by CABG has been decreasing and is currently at about 10%. Still, it needs to be emphasized that in the prospective randomized trials

complete revascularization by CABG was recommended and used in the majority of patients with three-vessel or left main coronary artery disease.[10-12,23] Furthermore the survival benefits both in these trials, as in previous coronary revascularization trials, have mainly been seen in patients with indications of multi-vessel disease.[174] Therefore, until the results of prospective trials directly comparing PCI with DES versus CABG in the three-vessel and left main disease population become available, CABG should be maintained as a preferred alternative for these patients. In the urgent setting. However, the raised risk of bleeding with CABG, in the presence of irreversible dual antiplatelet treatment, often leads to preference of PCI in order to avoid delay with revascularization. Although dual antiplatelet regimen is only a relative contraindication to early CABG, a cessation of platelet inhibition for 5 to 7 days, with the inherent risk of new events, currently is recommended before surgery.[154] Also other risk factors for complications at CABG will influence the indication (e.g., age, gender, diabetes mellitus, renal dysfunction, mental and general condition). Therefore in patients with three-vessel or left main disease there are several options that might be considered (i.e., CABG, PCI with DES of most lesions, or a staged procedure with PCI of the culprit lesion and later reassessment of the need for revascularization of other lesions). The final decision on the most appropriate revascularization method in the individual patient will be up to the judgment of the treating physician in relation to the circumstances—and also considering the patient preferences. In patients with one to two lesions, PCI will be the preferred alternative in the vast majority of cases with non–ST-elevation ACS.

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CHAPTER 28

Percutaneous Coronary Intervention and Concomitant Antithrombotic Therapy

Jon-David R. Schwalm and Shamir R. Mehta

Interventional cardiology has evolved significantly since the first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1977.[1] Advances in stent technology, delivery systems, and peri-procedural medical therapy have significantly improved clinical outcomes, broadened the target population, and reduced significant complications including abrupt vessel closure, stent thrombosis, and restenosis.

Percutaneous coronary intervention (PCI) can play an important role in the management of stable angina, unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), with more than 664,000 procedures performed in the United States in 2003.[2] In the past, debate regarding an initial conservative versus invasive approach for the management of UA/NSTEMI flourished. However, meta-analyses of recent randomized trials and subsequent guidelines support a routine invasive strategy in higher risk patients with UA or NSTEMI.[3-5]

Patients presenting with UA/NSTEMI pose a particular challenge to clinicians, given the wide variety of available antithrombotic options, each supported by recent evidence. This chapter will help guide clinicians through an evidence-based approach for the use of peri-PCI antithrombotic therapy in the setting of UA/NSTEMI. The specifics of individual antiplatelet and anticoagulant therapies are described in detail in Section 4.

PRE–PERCUTANEOUS CORONARY INTERVENTION ANTITHROMBOTIC THERAPY

Antiplatelet Therapy

Aspirin

Aspirin is a class 1 (Level of evidence A) recommendation for all patients presenting with UA/NSTEMI, regardless of whether or not they are scheduled to undergo PCI.[6] Aspirin therapy in the setting of UA/NSTEMI offers a 46% reduction in the combined outcome of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular (CV) death.[7] In the setting of PCI, initial studies with aspirin alone or in combination with dipyridamole have been shown to significantly reduce the need for revascularization and MI.[8,9] An initial loading dose of 162 to 325 mg of non-enteric coated aspirin is recommended for rapid absorption at the time of presentation with UA/NSTEMI.[6,10] However, despite multiple trials demonstrating the benefit of aspirin in the setting of UA/NSTEMI, the most appropriate maintenance dose is yet to be determined.

In an effort to understand the impact of aspirin dosing, the Antithrombotic Trialists' Collaboration (ATC) overview made indirect comparisons between trials evaluating different aspirin doses versus placebo.[7] They found that the relative benefit of aspirin was no greater in the trials evaluating higher doses of aspirin versus placebo compared with the trials evaluating lower doses of aspirin (<100 mg/day) versus placebo. A low dose is commonly used based on these results, and two observational analyses evaluating aspirin dose in acute coronary syndromes (ACS) suggested that bleeding risks increase with increasing aspirin dose with no improvement in efficacy outcomes.[11,12]

The CURRENT-OASIS 7 trial is a large randomized comparison of aspirin dosing in 25,000 patients with ACS.[13] After receiving a loading dose of at least 300 mg on day 1, patients with UA/NSTEMI or STEMI will be randomized to receive either high-dose aspirin (≥300 mg) versus low-dose aspirin (≤100 mg) for 30 days. There was no significant difference between higher-dose versus low-dose aspirin in the primary outcome of cardiovascular death, myocardial (re)-infarction or stroke at 30 days (4.2% vs. 4.4%; HR 0.97; 95% CI 0.86-1.09; $P = 0.61$).[13]

Thienopyridines

Thienopyridines, including ticlopidine, clopidogrel, and prasugrel, are a separate class of antiplatelet agents recommended in the management of patients with UA/NSTEMI as well as in patients undergoing PCI. Thienopyridines are used in conjunction with aspirin therapy.

A meta-analysis of the early studies with aspirin and ticlopidine demonstrated a

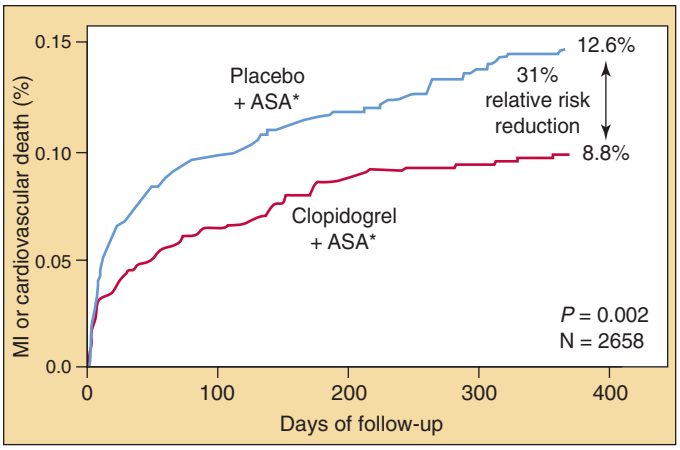

FIGURE 28–1 PCI-CURE: Composite of MI or cardiovascular death from randomization to end of follow-up in PCI patients with ACS. *(From Mehta SR, Yusuf S, Peters RJ, et al for the CURE Investigators: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-533.)*

reduction in stent thrombosis and bleeding complications when compared with warfarin.[14-19] However, hematologic side effects, including neutropenia and agranulocytosis, are of concern and limit the use of ticlopidine.[20] Ticlopidine was subsequently replaced by the more favorable side-effect profile of clopidogrel. Ticlopidine remains an acceptable alternative in peri-PCI patients with a clopidogrel allergy.

In the CAPRI study, clopidogrel monotherapy was at least as effective as aspirin for secondary prevention in patients with prior MI, prior stroke, or peripheral arterial disease.[21] In patients with UA/NSTEMI, the CURE trial demonstrated a significant 20% reduction in the combined outcome of CV death, MI, or stroke when clopidogrel was compared with placebo, on top of background therapy with aspirin (Fig. 28-1).[6,22] The benefits of clopidogrel became apparent early, with a reduction in ischemia as early as 24 hours after the loading dose was given. There was also a significant benefit of clopidogrel in reducing the composite of death, MI or stroke from day 30 to 1 year, suggesting that the optimal duration of therapy should be for 1 year.[23] An increased risk of major bleeding, but not life-threatening bleeding, was also observed in the dual antiplatelet therapy group. The risk of major bleeding seemed to be related to the aspirin dose, with higher doses increasing bleeding complications without improving benefit.[11]

Overall, there was no significant increase in bleeding in patients undergoing coronary artery bypass surgery (CABG) in the CURE study.[22] However, most patients had stopped clopidogrel for various time periods prior to CABG. When clopidogrel was stopped more than 5 days prior to CABG (5 days is the biological half-life of clopidogrel), there was no excess in major bleeding, as defined by the CURE trial criteria. When clopidogrel was continued to within 5 days of CABG, there was an increased major bleeding risk (relative risk [RR], 1.55, $P = .06$).[22] Therefore, in the minority of patients who require CABG surgery after ACS, it is recommended, if possible, that clopidogrel be withheld for about 5 days prior to surgery. Of the approximately 8% of ACS patients who require CABG, only a small portion require emergent surgery (<1%-2%), allowing clopidogrel to be withheld safely prior to the procedure in the majority.[24] A strategy of delaying the administration of clopidogrel until after the coronary anatomy is defined would allow withholding of clopidogrel in the small number of patients requiring emergent surgery, but would deprive the majority of patients (>95%) the potential benefits of early treatment.[23]

In patients requiring emergent CABG surgery who are on clopidogrel, several general recommendations can be considered. First, if possible, the surgery should be delayed for at least 24 hours from the last dose of clopidogrel, as the pharmacologic half-life of the active metabolite is less than 24 hours. If a platelet transfusion is necessary because of increased intraoperative bleeding or oozing, the newly transfused platelets should be functional as there would be no active metabolite present in the circulation. Second, after the surgery, tranexamic acid, which is an antifibrinolytic agent, can be considered. Finally, in cases were there is evidence of active bleeding, red blood cells and fresh frozen plasma or cryoprecipitate transfusion can be considered. The threshold for using these blood products will differ, depending on the center and the surgeon performing the procedure.

Pretreatment with clopidogrel (i.e., early initiation of clopidogrel before a PCI procedure) was evaluated in three studies: PCI-CURE, CREDO, and PCI-CLARITY.[25-27] The PCI-CURE and PCI-CLARITY trials were predefined, postrandomization subgroup analyses of patients undergoing PCI in the CURE and CLARITY trials, respectively.[22,25,27,28] CREDO was a standalone randomized trial of patients undergoing PCI for mostly stable angina.[26] In the PCI-CURE trial, there was a 30% reduction in CV death, MI, or urgent revascularization at 30 days with clopidogrel pretreatment, and in the PCI-CLARITY trial, there was a 46% reduction in CV death, MI, or stroke at 30 days.[25,27] The CREDO study suggested that pretreatment with clopidogrel at a 300-mg loading dose, should be administered at least 6 hours and ideally 15 hours prior to PCI, for optimal platelet inhibition and clinical benefit.[26] Analysis of in vitro and small randomized clinical trials have suggested that a loading dose of 600 mg can achieve maximal platelet inhibition within 2 hours and improve clinical outcomes, without an associated increased bleeding risk in patients undergoing PCI for both stable angina and UA/NSTEMI.[29-31] Therefore, given the significant clinical benefit of pretreatment with clopidogrel prior to PCI and the minimal risk of bleeding in the few patients advanced for CABG as outlined above, a clopidogrel loading dose of 300 mg at the time of presentation with UA/NSTEMI is strongly recommended. The CURRENT OASIS 7 trial is a randomized, double blind comparison of a higher loading and maintenance dose regimen of clopidogrel (600 mg followed by 150 mg maintenance dose for 1 week, then 75 mg daily) versus the standard dosing regimen of 300 mg followed by 75 mg daily.[13] 25,086 patients with an acute coronary syndrome referred for an invasive strategy underwent randomization. The primary outcome of cardiovascular death, myocardial (re)-infarction or stroke at 30 days occurred in 4.2% in the double-dose clopidogrel group and 4.4% in the standard-dose group (hazard ratio [HR] 0.94; 95% CI 0.83-1.06; $P = 0.30$). Major bleeding was 2.5% in the double-dose group and 2.0% in the standard-dose group (HR 1.24; 95% CI 1.05-1.46; $P = 0.012$). In the large number of patients who underwent PCI ($N = 17,263$), there was a significant reduction in the secondary outcome of stent thrombosis with double-dose clopidogrel (1.7% vs. 2.4%; HR 0.69; 95% CI 0.56-0.86; $P < 0.001$).[13]

Recent observational data support the notion that a poor pharmacodynamic response to clopidogrel is associated with a higher risk of adverse ischemic events.[32-44] The response to clopidogrel, as measured by platelet aggregation studies, takes on a normal distribution, with the majority having a good response, and small number having a poor response or hyper-response. One approach to dealing with clopidogrel response variability could be to measure platelet function using a reliable assay. If the patient is found to be a poor responder, the dose of clopidogrel could be increased or an alternative thienopyridine such as prasugrel could be considered. If the patient has an adequate response, the standard dose of clopidogrel can be used. This approach requires

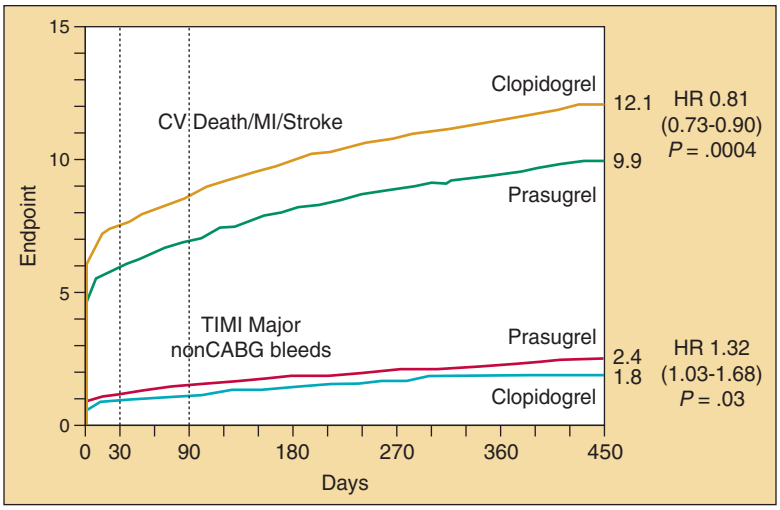

FIGURE 28–2 Triton-TIMI 38: Cumulative Kaplan-Meies estimates for the primary efficacy and safety end-points during the follow-up period. *(From Wiviott SD, Braunwald E, McCabe CH, et al for the Triton-TIMI 38 investigators: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.)*

evaluation in randomized trials before being widely recommended. At least one randomized trial, the GRAVITAS trial, is currently evaluating this approach using the VerifyNow purinergic G protein–coupled P2Y 12 (P2Y12) receptor assay.[45]

Prasugrel is the newest thienopyridine to be studied. Like clopidogrel, it is a pro-drug that is metabolized by the cytochrome P-450 system in the liver. However, the metabolism of prasugrel into the active metabolite is more efficient, resulting in higher levels of the active metabolite producing a more rapid and potent antiplatelet effect with less inter-individual variability in response.[46] This pharmacodynamic profile may be favorable, especially when prompt platelet inhibition is required in the peri-PCI setting. The Triton-TIMI 38 trial, evaluating 13,608 patients undergoing PCI in the setting of NSTEMI and STEMI, showed a significant clinical benefit in the primary outcome of CV death, MI, or stroke at 15 months with prasugrel therapy when compared with standard dose clopidogrel (9.9% vs. 12.1%, $P < .001$) (Fig. 28-2).[47] In addition, prasugrel resulted in a 1.3% absolute risk reduction ($P < .001$) in definite or probable stent thrombosis (Fig. 28-3). There was a significant increase in TIMI major bleeding, life-threatening bleeding, and fatal bleeding in the prasugrel group. The Triton-TIMI 38 trial compared a 60-mg loading dose of prasugrel to a 300-mg load of clopidogrel. Whether the clinical benefits achieved would have been observed if prasugrel was compared with a 600-mg clopidogrel loading dose followed by a 150-mg maintenance dose is not known. The lack of pretreatment in this trial may also have disadvantaged clopidogrel. Nevertheless, the results of the Triton trial do suggest that faster and greater inhibition of platelet function will result in improved efficacy outcomes at the cost of an increase in bleeding complications.

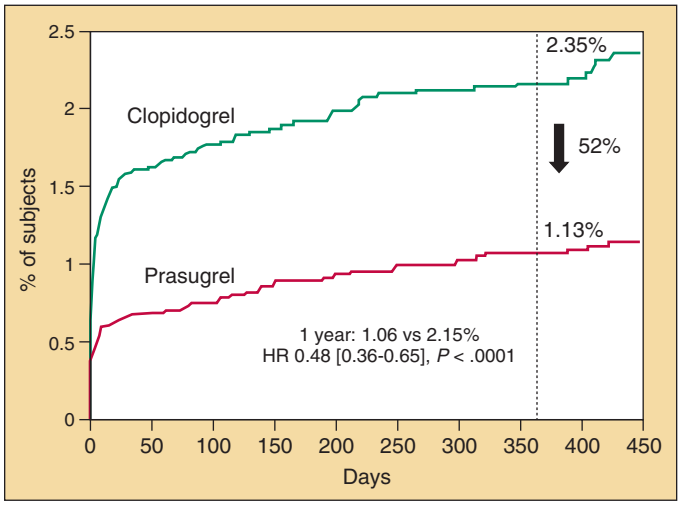

FIGURE 28–3 Triton-TIMI 38: Definite/probable stent thrombosis at 1 year ($N = 12,844$). *(From Wiviott SD, Braunwald E, McCabe CH, et al for the Triton-TIMI 38 investigators: N Engl J Med 2007;357:2001-2015.)*

Ticagrelor is a reversible, non-thienopyridine, direct-acting inhibitor of the adenosine diphosphate receptor (P2Y12). It is a promising new oral antiplatelet agent evaluated in the management of patients presenting with an ACS, with or without ST-segment elevation. The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial randomized 18,624 patients to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300-600 mg loading dose, 75 mg daily thereafter) (Fig. 28-4).[47a] Study drug was administered early and, in contrast to the TRITON study, before coronary angiography. Approximately 60% of all patients underwent PCI during the index hospitalization. The primary end-point (a composite of death from vascular causes, myocardial infarction, or stroke) was significantly reduced in patients receiving ticagrelor (9.8% vs. 11.7%, $P < 0.001$).[47a] These benefits were observed early (i.e., within the first 30 days) and later (after 30 days to 1 year). In addition, ticagrelor resulted in lower rates of death due to vascular causes (4.0% vs. 5.1%, $P = 0.001$) and myocardial infarction (5.8% vs. 6.9%, $P = 0.005$). Definite stent thrombosis was also reduced with ticagrelor (1.3% vs. 1.9%, $P = 0.009$). Consistent reductions in the primary outcome were observed in patients scheduled to undergo an invasive strategy. The rates of total major bleeding did not differ between ticagrelor and clopidogrel (11.6% and 11.2%, respectively; $P = 0.43$), however ticagrelor was associated with a higher rate of major bleeding in the majority of patients not undergoing CABG surgery (4.5% vs. 3.8%, $P = 0.03$).[47a] Compared with clopidogrel, ticagrelor was associated with a higher rate of ventricular pauses more than 3 seconds (5.8% vs. 3.6%, $P = 0.01$) and was more frequently associated with dyspnea (13.8% vs. 7.8%, $P < 0.001$), including dyspnea resulting in discontinuation of study drug (0.9% vs. 0.1%, $P < 0.001$). The data were consistent in most of the large number of pre-specified subgroups, with the exception of region. In those patients

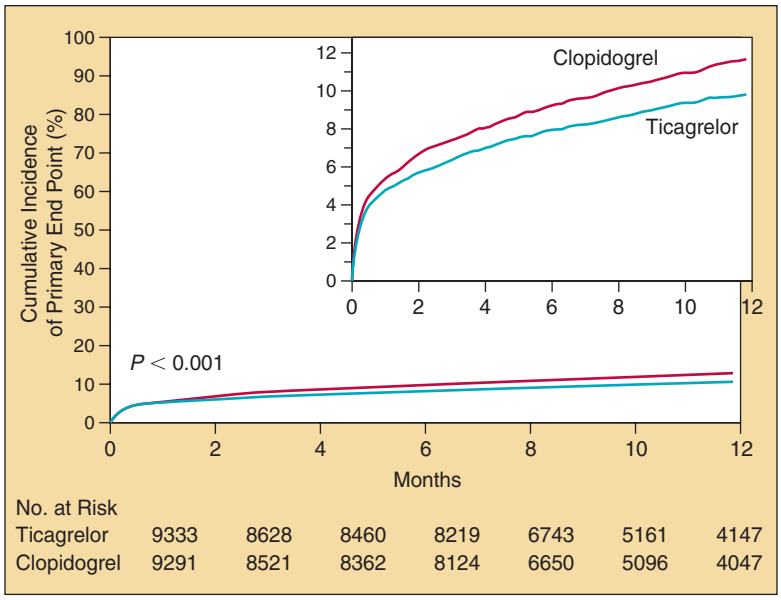

FIGURE 28–4 Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point. The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P < 0.001). *(From Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.)*

enrolled in North America, there appeared to be nominally significant heterogeneity ($P < 0.05$) with an apparent worse outcome with ticagrelor versus clopidogrel (data) compared with the rest of the world.[47a] While this result was most likely due to the play of chance, other possible explanations (such as variations in aspirin dose) need to be excluded.

Glycoprotein IIb/IIIa Receptor Antagonists

Glycoprotein (GP) IIb/IIIa receptor antagonists are another class of antiplatelet agents frequently used in the management of patients undergoing PCI and presenting with UA/NSTEMI. A meta-analysis of more than 12,000 patients with UA/NSTEMI demonstrated a reduction in death and nonfatal MI when treated with a GP IIb/IIIa antagonist.[48] Furthermore, the evidence suggests an independent mortality reduction in diabetic patients with UA/NSTEMI and undergoing PCI.[49] Because the majority of evidence supporting the use of GP IIb/IIIa was published prior to the addition of clopidogrel therapy, the role of adding a GP IIb/IIIa antagonist on top of treatment with aspirin and clopidogrel has been debated.[48,49] The ISAR-REACT-2 trial demonstrated a significant benefit with the combination of abciximab (0.25 mg/kg bolus followed by a 12-hour infusion of 0.125 µg/kg per min, maximum 10 µg/min), and clopidogrel pre-treatment compared to clopidogrel alone. However, the reduction in the composite of death, MI, and urgent target vessel revascularization at 30 days was only noted in troponin-positive patients undergoing PCI.[50] The ISAR-REACT-2 trial also demonstrated that low to moderate risk ACS patients can be safely treated with clopidogrel and aspirin as the only antiplatelet agents.[50] The 2005 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) PCI guidelines suggest that GP IIb/IIIa antagonist should be administered either "upstream" or in the catheterization laboratory if there is no pre-treatment with clopidogrel (Class 1, Level of Evidence A).[51] The more recent 2007 ACC/AHA acute coronary syndrome guidelines suggest either GP IIb/IIIa or clopidogrel may be used in addition to aspirin therapy for the pre-treatment of lower risk patients presenting with UA/NSTEMI and undergoing PCI (Class I, Level of Evidence A).[6] For multiple reasons, including lower cost, need for long-term clopidogrel therapy post PCI, and clinical benefit, clopidogrel is preferred over GP IIb/IIIa agents in lower risk patients presenting with UA/NSTEMI and undergoing PCI. However, given the results of the ISAR-REACT-2 trial, guidelines suggest that both agents in combination with aspirin therapy should be used for higher risk, troponin-positive, ACS patients undergoing PCI.[6,50] Appropriate patient selection is required prior to the initiation of GP IIb/IIIa inhibitors, given the majority of benefit is noted in troponin-positive and diabetic patients with UA/NSTEMI. Furthermore the timing of GP IIb/IIIa inhibitor use peri-PCI in the setting of patients presenting with UA/NSTEMI has been evaluated in the Acuity Timing trial.[52] A deferred strategy at time of PCI, rather than an upstream approach to GP IIb/IIIa inhibitor use was not significantly different with respect to the composite ischemic events ($P = .13$).[52] However, the deferred approach to GP IIb/IIIa inhibitor use resulted in a significant reduction in 30-day rates of major bleeding (4.9 vs. 6.1%, $P = .009$ for superiority).[52]

In summary, there are several options for antiplatelet therapy in the treatment of UA/NSTEMI patients scheduled for early revascularization with PCI. Given the evidence to date, the ideal antiplatelet regimen must include aspirin (minimum 160 mg load and 81 mg daily). Early initiation of clopidogrel has proven benefits in all patients (low, intermediate, and high risk) presenting with UA/NSTEMI, whether or not they undergo PCI. Therefore, clopidogrel pre-treatment with a minimum loading dose of 300 mg should be instituted in the majority of patients with UA/NSTEMI. The addition of GP IIb/IIIa inhibitor is indicated in patients presenting with UA/NSTEMI and undergoing PCI if one of the following criteria is met: diabetes, troponin-positive acute coronary syndrome, or no pretreatment with clopidogrel.

Anticoagulation Therapy

Unfractionated Heparin

Unfractionated heparin (UFH) is the most widely used anticoagulant for both the conservative and invasive management

of patients presenting with UA/NSTEMI (Class 1, Level of Evidence A).[6] However, the majority of the evidence evaluating UFH was prior to therapies currently used in the management of patients presenting with ACS. Unfractionated heparin (UFH) has minimal renal clearance and usually does not require dose adjustment in patients with reduced creatinine clearance. When added to aspirin, UFH has been shown to almost halve the rates of death and recurrent MI compared with aspirin alone in patients presenting with UA/NSTEMI.[53] UFH is most effective when administered as a weight-based bolus and subsequent IV infusion (60 U/kg initial bolus followed by an infusion of 12 U/kg per hour, adjusted to a goal activated partial thromboplastin time [aPTT] of 50 to 70 seconds).[54] Upstream use of UFH prior to PCI is only indicated in patients presenting with an ACS. Elective PCI patients do not require upstream treatment with UFH.

Low–Molecular-Weight Heparin

Low–molecular-weight heparin (LMWH), and more specifically enoxaparin, is well established in the management of patients presenting with UA/NSTEMI (Class 1, Level of Evidence A).[6] Enoxaparin offers benefits including less heparin induced thrombocytopenia (HIT) and ease of administration (twice daily, subcutaneous dosing at 1 mg/kg), without the need for regular monitoring. However, because of its renal clearance, enoxaparin requires careful dose adjustments in the setting of reduced creatinine clearance and this may prohibit its use in some patients with significant renal dysfunction. Early trials of enoxaparin in patients treated with a conservative strategy suggested an overall clinical benefit with respect to death, MI, and recurrent angina when compared to UFH.[55-57] However, these trials employed a conservative strategy and were conducted before the use of clopidogrel and GP IIb/IIIa inhibitors. One trial has demonstrated the benefit of enoxaparin in patients receiving eptifibatide.[58] More recent trials, including A to Z and SYNERGY, incorporating PCI and the use of adjuvant antiplatelet agents, did not demonstrate superiority of enoxaparin when compared with UFH and suggested an increase in bleeding complications.[59,60]

Fondaparinux

Fondaparinux is an indirect parenteral factor Xa inhibitor that is recommended for the management of patients presenting with UA/NSTEMI (Class 1, Level of Evidence B).[6] Fondaparinux is administered as a once a day subcutaneous injection of 2.5 mg. In the large scale OASIS 5 randomized controlled trial (N = 20,078), fondaparinux was proven to be non-inferior to enoxaparin for efficacy, but there was a 50% reduction in bleeding, resulting in a highly significant net clinical benefit favoring fondapairnux.[61] Moreover, the reduction in bleeding translated into a significant reduction in mortality in the fondaparinux group.[61] Fondaparinux was superior to enoxaparin in terms of bleeding reduction at all levels of renal function (patients with a serum creatinine level of at least 3 mg per deciliter or 265 μmol per liter were excluded from the trial), with the greatest benefit in those with lowest renal function.[62] The majority of patients in OASIS 5 were managed with an invasive strategy and of these, about 40% underwent PCI.[61] In patients undergoing PCI, there was a significant reduction in the combined endpoint of death, MI, stroke, major bleeding, or any procedural complication in the fondaparinux group compared with the enoxaparin group (16.6% vs. 20.6%, $P < .001$).[61] Further, the reduction in bleeding was observed as early as the first day after randomization, suggesting that a very short duration of fondaparinux was beneficial. Because fondaparinux inhibits only factor Xa, with no effect on thrombin, it is recommended that adjunctive intravenous UFH (50-60 IU/kg) be administered at the time of PCI. This is to protect against contact induced activation of the coagulation system, which can occur less than 1% of the time with fondaparinux. In the OASIS 5 trial, the use of adjunctive UFH did not appear to increase the bleeding risk and works well with fondaparinux given upstream.[57] Therefore, fondaparinux is recommended over enoxaparin for all patients presenting with UA/NSTEMI, regardless of intervention, as per the 2007 European Society of Cardiology guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes.[63] The ACC/AHA UA/NSTEMI guidelines also list fondaparinux as a class 1 recommendation for both an invasive and a conservative management strategy, making it an ideal agent for early treatment of UA/NSTEMI (i.e., in the emergency room) when ultimate management strategy and need for revascularization is not known until diagnostic coronary angiography has been performed.[6]

Direct Thrombin Inhibitors

Bivalirudin is a direct thrombin inhibitor that has been evaluated in the management of patients with UA/NSTEMI and in patients undergoing PCI. The use of bivalirudin in stable and ACS patients undergoing PCI was evaluated in the REPLACE 2 and the ISAAR-REACT 3 trials, respectively.[64,65] The REPLACE-2 trial evaluated more than 6000 patients undergoing both elective and urgent PCI. Bivalirudin with provisional GP IIb/IIIa was found to be non-inferior to UFH with planned GP IIb/IIIa with respect to the combined primary outcome of death, MI, or urgent repeat revascularization.[64] There was a significant reduction in major bleeding in the bivalirudin group (2.4 vs. 4.1%, $P < .001$).[64] The ISAAR-REACT 3 trial compared bivalirudin monotherapy with UFH monotherapy in patients with ACS undergoing PCI.[65] All patients were pretreated with 600 mg of clopidogrel at least 2 hours prior to PCI. The bivalirudin group was no different than UFH with respect to the primary outcome of net clinical benefit.[65] Major bleeding was lower with bivalirudin compared with UFH, but this may have been because the bolus dose of UFH used in the trial (140 IU/kg) was much higher than the upper limit of guideline recommended doses.

Finally bivalirudin monotherapy was compared with bivalirudin plus GP IIb/IIIa inhibitor, or UFH/enoxaparin plus GP IIb/IIIa inhibitor in patients with UA/NSTEMI undergoing an invasive strategy in the ACUITY trial.[52,66] The composite endpoint of death, MI, and unplanned revascularization at one year was not statistically different between the three groups, with 15.4% in the UFH/enoxaparin plus GP IIb/IIIa inhibitor group, 16% in the bivalirudin plus GP IIb/IIIa inhibitor group, and 16.2% in the bivalirudin monotherapy group (P = .29). In patients pretreated with clopidogrel, bivalirudin alone demonstrated a significant reduction in major bleeding consistent with previous trials and was found to be non-inferior to UFH or enoxaparin plus GP IIb/IIIa with respect to the net clinical benefit.[52,66] Given bivalirudin, in conjunction with clopidogrel pretreatment, has been demonstrated to be as effective as UFH or enoxaparin plus GP IIb/IIIa in low to high risk ACS patients undergoing PCI, it is recommended in the invasive management of patients presenting with UA/NSTEMI (Class 1, Level of Evidence B).[6] Bivalirudin is also a reasonable alternative for patients with a heparin allergy or HIT.

In summary, there are various anticoagulant agents including UFH, fondaparinux, enoxaparin, or bivalirudin, all indicated in the treatment of patients with UA/NSTEMI. The appropriate choice of anticoagulation therapy depends on various factors including the management strategy and timing of invasive intervention, the patient's individual bleeding risk, renal function, level of clopidogrel pretreatment prior to PCI, and overall risk at time of presentation with UA/NSTEMI.

PERI–PERCUTANEOUS CORONARY INTERVENTION ANTITHROMBOTIC THERAPY

Antiplatelet Therapy

Most patients undergoing PCI should ideally be pretreated with aspirin and clopidogrel at the time of first presentation to hospital. At the time of PCI, an additional 300 mg of clopidogrel, for a total loading dose of 600 mg, can be administered to ensure adequate platelet inhibition. The evidence suggests that a 600-mg load of clopidogrel in stable elective patients administered at the time of PCI is safe and effective.[67] The CURRENT-OASIS 7 trial provides evidence for the benefit of an increased loading and maintenance dose of clopidogrel in patients with ACS undergoing PCI. The increased loading dose (600 mg) followed by 150 mg on days 2-7 then 75 mg daily) when compared to the standard dose regimen of clopidogrel (300 mg load then 75 mg daily) significantly reduced the primary outcome of cardiovascular death, myocardial (re)-infarction, or stroke at 30 days (3.9% vs. 4.5%; adjusted HR 0.86, 95% CI, 0.74-0.99, $P = 0.039$). Definite stent thrombosis was also reduced by 46% (0.7% vs 1.3%, HR 0.54, 95% CI 0.39-0.74, $P = 0.0001$).[13] Given the favorable clinical benefit, as evidenced by the TRITON-TIMI 38 trial, and the significant reduction in definite or probable stent thrombosis, prasugrel will play an important antiplatelet role in the peri-PCI management of patients presenting with UA/NSTEMI (see Figs. 28-2 and 28-3).

At least one large-scale randomized trial has suggested that the initiation of GP IIb/IIIa inhibitor can be safely deferred until the time of PCI.[52,68] By targeting GP IIb/IIIa inhibitors to higher risk patients undergoing PCI, their benefits are maximized and their bleeding risks are minimized.[69]

Anticoagulation Therapy

Of the three options for anticoagulation during PCI (UFH, enoxaparin or bivalirudin), UFH has been the most commonly used since the introduction of PTCA. In the setting of PCI, UFH has been demonstrated to reduce thrombus and subsequent abrupt vessel closure.[70] When used in combination with GP IIb/IIIa inhibitor, a reduced dose of heparin targeting an activated clotting time (ACT) of 200 to 250 seconds, rather than 250 to 300 seconds with UFH alone has demonstrated a reduced risk of bleeding complications.[71-73]

The appropriate dosing of enoxaparin peri-PCI has been evaluated in both the STEEPLE and SYNERGY trials.[60,74] In the STEEPLE trial, patients were randomized to either enoxaparin (0.5 mg/kg or 0.75 mg/kg as one IV dose prior to PCI) versus UFH in elective patients undergoing PCI.[74] Numerically higher mortality was noted in the 0.5 mg/kg arm and there was no significant difference in the primary outcome of major and minor bleeding in 0.75 mg/kg arm compared to UFH.[74] The SYNERGY trial compared enoxaparin to UFH in more than 10,000 patients presenting with UA/NSTEMI and managed with an early invasive strategy.[60] Patients in the enoxaparin group were treated with twice daily subcutaneous injections at 1 mg/kg. If enoxaparin was administered within 8 hours of PCI, no additional enoxaparin was given prior to PCI. However, if the last dose of subcutaneous enoxaparin was given more than 8 hours from PCI, then an additional IV dose of 0.3 mg/kg was administered just prior to PCI.[60] The SYNERGY trial demonstrated non-inferiority of enoxaparin compared to UFH in this patient population; however, there was a significant increase in TIMI major bleeding in the enoxaparin group (9.1% vs. 7.6%, $P = .008$).[60] Part of the increase in bleeding in the enoxaparin group may have been related to indiscriminate crossover to UFH (SYNERGY was an open label trial and investigators knew the treatment assignment). However, this could not account for all of the increased bleeding, as even patients who remained on consistent therapy with enoxaparin had a significantly increased risk of bleeding compared with UFH.

In patients undergoing PCI in the OASIS 5 trial, the combined rates of death, MI, and refractory ischemia were similar in both the enoxaparin and fondaparinux treated groups, as were the rates of coronary complications.[61] However, patients undergoing PCI in the fondaparinux group had significantly lower major bleeding complications (5.4% vs. 2.8%; RR, 0.51; 95% confidence interval [CI], 0.40-0.66) and a superior net clinical benefit when compared with enoxaparin.[61] For patients presenting with UA/NSTEMI who are initially treated with fondaparinux, a UFH bolus at the time of PCI is recommended to optimize procedural anticoagulation. Initial concerns regarding catheter thrombus in patients treated with fondaparinux, in the OASIS 5 study, were overcome with the administration of a UFH bolus at the time of PCI (0.013 mL/kg of UFH with the concomitant GP IIb/IIIa and 0.02 mL/kg of UFH without concomitant GP IIb/IIIa).[61] The optimal dose of UFH administered peri-PCI in patients pretreated with fondaparinux is being further evaluated in the on-going FUTURA-OASIS 8 trial.

If bivalirudin is to be used in place of UFH and a GP IIb/IIIa antagonist, it is important that the patient be pretreated with a thienopyridine prior to PCI in the setting of ACS. Bivalirudin may also be used in place of UFH if the patient has had prior HIT. The following regimen should be used: 0.75 mg/kg IV bolus, followed by a continuous infusion at 1.75 mg/kg/hour for the duration of procedure. The ACT should be determined 5 minutes after bolus dose with an additional bolus of 0.3 mg/kg if necessary.

POST–PERCUTANEOUS CORONARY INTERVENTION ANTITHROMBOTIC THERAPY

Antiplatelet Therapy

The appropriate antiplatelet regimen following PCI is paramount in preventing serious complications including stent thrombosis. Antiplatelet therapy has also been demonstrated to reduce major adverse cardiac events (MACE) in the setting of UA/NSTEMI as described above.

Aspirin is recommended indefinitely following PCI. Recent guidelines suggest that aspirin should be continued at a dose of 162 to 325 mg daily for 1 month following bare-metal stent (BMS) insertion, for 3 months following sirolimus-eluting stent (SES) insertion, and for 6 months following paclitaxel-eluting stent (PES) insertion.[5] Aspirin should then be continued at 75 to 162 mg daily thereafter. There is currently no evidence to suggest that higher dose aspirin is safer immediately post stent insertion as compared to lower dose aspirin. The efficacy of low-dose aspirin is similar to higher dose aspirin in preventing MACE and is associated with fewer bleeding complications.[7] The bleeding risk is further increased post-PCI, given the required addition of clopidogrel.[22] For these reasons, a low-dose regimen of aspirin (75-162 mg daily) could be considered following PCI. Furthermore, given the results from the CURRENT-OASIS 7 trial, either a low (≤100 mg) or higher dose (≥300 mg) regimen of aspirin are acceptable options following PCI.[13]

In patients presenting with UA/NSTEMI, evidence suggests that clopidogrel should be continued, at a dose of 75 mg, ideally for 12 months to derive optimal reductions in MACE, regardless of intervention.[22] In patients presenting with an ACS and undergoing PCI, a 7-day double-dose regimen of clopidogrel reduces major cardiovascular events and stent

TABLE 28–1 Suggested Algorithm for Adjunctive Antithrombotic Therapy*

Timing	Antithrombotic Therapy	Comment
Pre-PCI (Emergency room presentation/ time of diagnosis)	**Aspirin** (Minimum 160 mg load and 81 mg daily)	Consider clopidogrel alone for aspirin allergy
	Clopidogrel Minimum 300 mg load and 75 mg daily (consider 600 mg load and 150 mg for 1 week, then 75 mg daily)	Consider ticlopidine for clopidogrel allergy
	Anticoagulation (either):	
	UFH (60 U/kg bolus, 12 U/kg/hr infusion for goal aPTT of 50 to 70 seconds)	UFH if serum creatinine >3 mg/dL (265 µmol/L), continued up to 48-72 hours and/or discontinue at time of PCI
	Fondaparinux (2.5 mg sc daily)	
	Enoxaparin (1 mg/kg sc twice daily)	
Peri-PCI (After coronary anatomy defined)	**Prasugrel** (60 mg load and 10 mg daily)	Consider if no pretreatment with clopidogrel
	Anticoagulation:†	
	UFH	
	With GP IIb/IIIa	
	• 50-70 units/kg (ACT of 200 seconds)	
	Without GP IIb/IIIa	
	• 70-100 units/kg (ACT of 250-300 seconds)	
	With prior fondaparinux	
	• 50-60 IU/kg ± GP IIb/IIIa	
	Bivalirudin (0.75 mg/kg IV bolus, 1.75 mg/kg/hour infusion for the duration of procedure)	Patients should be pretreated with clopidogrel if bivalirudin is the anticoagulant of choice
	Enoxaparin (0.3 mg/kg IV if >8 hours since last dose)	
	Abciximab (GP IIb/IIIa) (0.25 mg/kg IV bolus then 0.125 µg/kg/min for 12 hours)	Indicated in patients with: diabetes, troponin-positive ACS, and no pre-treatment with clopidogrel
Post-PCI	**Aspirin** (Minimum 81 mg daily—indefinitely)	
	Clopidogrel (Minimum 75 mg daily for 1 year)	Consider continuation of clopidogrel therapy for >1 year with implantation of DES
	Prasugrel (10 mg daily for 1 year)	If clopidogrel not used

ACT, activated clotting time; aPTT, activated partial thromboplastin time.

*Suggested algorithm for the evidence-based use of adjunctive antithrombotic therapy for patients with unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI) referred for an invasive strategy.

†It is generally recommended that the anticoagulant selected pre-PCI is continued throughout the procedure with the exception of fondaparinux where the addition of UFH is recommended.

From Wiviott S, Braunwald E, McCabe C, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.

thrombosis compared with the standard-dose regimen.[13] In patients undergoing PCI, regardless of clinical presentation, clopidogrel is recommended for an absolute minimum of 1 month and ideally up to 12 months with BMS insertion.[5] For patients with drug-eluting stents (DES), both SES and PES, clopidogrel is recommended for an absolute minimum of 12 months.[5] More recently, concerns of increased very-late stent thrombosis (>1 year) with DES have been demonstrated in both randomized controlled trials and registry data.[75-77] The discontinuation of clopidogrel therapy has been identified as an independent predictor of stent thrombosis.[78] Therefore, patients presenting with UA/NSTEMI and undergoing PCI with a DES require clopidogrel for a minimum of 1 year and ideally indefinitely, as tolerated.

If GP IIb/IIIa inhibitors is initiated at the time of PCI, a 12-hour continuous infusion has been recommended.[50] However, a single center randomized controlled trial evaluated patients undergoing PCI (approximately 40% presenting with ACS) with bolus-only versus bolus and infusion of abciximab. There were no differences between the two groups with respect to MACE; however, the bolus-only group had significantly fewer bleeding complications and a shorter length of stay.[79] Given these results, a single bolus of abciximab at the time of PCI can be considered.

Anticoagulation Therapy

The majority of stable patients with UA/NSTEMI that are initially treated with IV UFH before and during PCI, may have this anticoagulant discontinued following uncomplicated PCI, provided there are no alternate indications for therapeutic anticoagulation. For patients treated with fondaparinux pre-PCI, this anticoagulant can be reinitiated at 2.5 mg daily until hospital discharge or a maximum of 8 days in patients presenting with UA/NSTEMI without increasing the risk of bleeding.[61] Patients treated with a bivalirudin strategy, depending on their coronary anatomy, bleeding risk, and clinical presentation may continue on the IV infusion at 1.75 mg/kg/hour for the duration of procedure and up to 4 hours post-procedure. If needed, the IV infusion may be continued at 0.2 mg/kg/hour for up to 20 hours.

CONCLUSION

In conclusion, patients presenting with UA/NSTEMI undergoing PCI should be treated with aspirin (minimum 160 mg load and 81 mg daily), clopidogrel (minimum 300 mg load and 75 mg daily), and an anticoagulant (either IV UFH, bivalirudin, fondaparinux, or enoxaparin). Intravenous UFH should be initiated if renal function is severely impaired (60 U/kg initial bolus followed by an infusion of 12 U/kg per hour, adjusted to a goal aPTT of 50 to 70 seconds) (Table 28-1).

Just prior to PCI, additional antithrombin therapy should be considered, depending on the choice of anticoagulation regimen initiated before PCI. Intravenous UFH (50-60 IU/kg) should be added if fondaparinux was started upstream (regardless of time from last subcutaneous dose). If IV UFH is the upstream anticoagulant of choice, then additional UFH may need to be added to target an ACT of 200 to 250 seconds with concomitant GP IIb/IIIa or 250 to 300 seconds without concomitant GP IIb/IIIa. If subcutaneous enoxaparin was given more than 8 hours from PCI, then an additional IV dose of 0.3 mg/kg should be administered. If bivalirudin was used pre-PCI, then 0.75 mg/kg IV bolus, followed by a continuous infusion at 1.75 mg/kg/hour for the duration of procedure is the recommended dosing strategy. GP IIb/IIIa inhibitors

should be considered as adjunctive antithrombotic therapy in patients with diabetes, troponin-positive ACS, or in those who did not receive pretreatment with a thienopyridine. Finally, a reload of 300 mg of clopidogrel immediately prior to PCI has been shown to further inhibit platelet function (see Table 28-1).

Following PCI, patients should continue on aspirin (minimum 81 mg daily) indefinitely. Clopidogrel should be continued for 1 year at 75 mg daily. With DES implantation, clopidogrel could be continued longer than 1 year, if tolerated, given the concern of very late stent thrombosis.

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CHAPTER 29

Bleeding in the Acute Coronary Syndromes

Michael W. Tempelhof and Sunil V. Rao

The mortality rate from coronary heart disease (CHD) in the United States has decreased 40% over the past two decades.[1] About half of this mortality benefit is attributed to advancements in the efficacy and utilization of synergistic antiplatelet agents, anticoagulant therapies, and invasive risk stratification in high-risk patients with acute coronary syndrome (ACS; unstable angina, [UA] non–ST-segment elevation myocardial infarction [NSTEMI]).[2-4] Although this paradigm in the management of ACS minimizes ischemic events, it also increases the risk of bleeding and the need for blood transfusion.[5-8] Recent analyses and randomized controlled trials demonstrate an independent association between bleeding complications, blood transfusions, and poor outcomes among patients with ACS.[9-13] Management strategies that provide adequate reductions in ischemia while minimizing the risk of bleeding and need for transfusion therefore have the potential to improve outcomes associated with ACS. Clinical trials of antithrombotic therapies associated with decreased bleeding complications have demonstrated improvements in short-term and long-term survival. This chapter addresses the clinical importance of bleeding complications and blood transfusion associated with an ACS. Bleeding event rates, associations between bleeding and clinical outcomes, cause of bleeding and transfusion with adverse outcomes, and recommendations for the management and prevention of bleeding complications among ACS patients will be discussed.

REPORTED INCIDENCE OF BLEEDING COMPLICATIONS

Influence of Definition and Treatment Strategies

The reported incidence of major bleeding events in the ACS period varies significantly across clinical trials with best estimates between less than 1% and 14%.[14-27] Numerous factors account for the discrepancy among trials and registries. Currently, no standard definition of bleeding severity exists. Second, bleeding rates have been directly correlated with the increased utilization of invasive revascularization procedures. Therefore, trials that employ a more conservative approach may have correspondingly lower rates of observed bleeding. Moreover, clinical trials of anticoagulant and antiplatelet therapies use various combinations of agents, which may also affect the measured rate of bleeding.[8,22] Recent trials, representing a more aggressive antiischemic treatment approach (reflected as concomitant use of multiple antiplatelet and antithrombin agents) may contribute to the higher reported incidence of bleeding during an ACS event. Finally, differences in an individual patient's propensity to experience a bleeding event may also contribute to the observed variance in bleeding incidence during an ACS.[26,27]

The existence of multiple bleeding definitions accounts in part for the disparity of the reported incidence of bleeding complications among ACS patients. Historically, the two most commonly employed bleeding severity classification schemes are the TIMI and GUSTO scales.[28,29] The GUSTO scale categorizes bleeding as severe or life-threatening, moderate, mild, or none, and defines bleeding based on clinical outcomes such as hemodynamic compromise or intracranial hemorrhage. In contrast, the TIMI definition categorizes bleeding as major, minor, minimal, or none and is dependent on changes in laboratory parameters (hemoglobin or hematocrit) and not necessarily on clinically defined events (although intracranial hemorrhage is considered a TIMI major bleed). The use of different bleeding definitions across studies can influence the reported incidence of bleeding (Table 29-1). Additional definitions of bleeding events adopt variations[27,30,31] and combinations[32] of the GUSTO and TIMI classification schemes, such as those developed in the SYNERGY,[25] PURSUIT,[8] and OASIS-5[20] trials. These trials uniquely defined bleeding events with combinations of both clinical and laboratory findings. ACS trial-specific definitions for bleeding complications have been developed, such as those in FRISC,[33] ESSENCE,[23] CURE,[22] and ACUITY[21] trials. Variations in transfusion thresholds, reductions in hemoglobin, and interruption of treatment

TABLE 29–1 Sample Bleeding Definitions Across Clinical Trials of Acute Coronary Syndrome or Percutaneous Coronary Intervention[77]

Trial	Patient Population	Intervention	Bleeding Definition
SYNERGY	NSTE-ACS	Enoxaparin vs. heparin	TIMI & GUSTO
PURSUIT	NSTE-ACS	Eptifibatide/heparin vs. heparin	TIMI & GUSTO
CURE	NSTE-ACS	Aspirin vs. aspirin plus clopidogrel	**Major bleeding** • Life-threatening (fatal, intracranial, requiring surgical intervention, results in hypotension, decrease in Hgb ≥5 g/dL, or required ≥4 units of blood) • Other major bleeding episodes (requiring transfusion of 2 or 3 units, intraocular) **Minor bleeding** • Led to discontinuation of study drug
GUSTO IIb	NSTE-ACS	Hirudin vs. heparin	GUSTO
OASIS-2	NSTE-ACS	Hirudin vs. heparin	**Major bleeding** • Life-threatening (fatal, intracranial, requiring surgical intervention or ≥4 units of blood or plasma expanders) • Other major bleeding episodes (requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood or judged to be disabling) • All other bleeding events classified as minor
OASIS-5	NSTE-ACS	Fondaparinux vs. enoxaparin	**Major bleeding** • Fatal, intracranial, retroperitoneal, intraocular leading to vision loss • Decrease in Hgb ≥3 g/dL adjusted for transfusion • Transfusion of 2 units of red blood cells or equivalent whole blood **Minor bleeding** • Any other clinically significant bleeding not meeting major criteria leading to study drug interruption, surgery, or transfusion of 1 unit of blood
ACUITY	NSTE-ACS	Bivalirudin alone vs. heparin or enoxaparin plus GP IIb/IIIa vs. bivalirudin plus GP IIb/IIIa	**Major bleeding** • Intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, a reduction in hemoglobin levels of at least 4 g/dL without an overt bleeding source or at least 3 g/dL with such a source, reoperation for bleeding, or transfusion of a blood product
CRUSADE	NSTE-ACS	Blood transfusion	**Major bleeding** • An absolute decrease in hematocrit concentration by 12% from baseline, intracranial hemorrhage, retroperitoneal bleeding, or a RBC transfusion due to bleeding
GRACE	NSTE-ACS		• Life-threatening bleeding requiring a transfusion of >2 units of RBC, resulting in a decrease in hematocrit of >10%, occurring intracerebrally, or resulting in stroke or death
TRITON TIMI 38	NSTE-ACS		• Life-threatening bleeding category defined as a TIMI major bleeding event that is fatal, leads to hypotension requiring treatment with intravenous inotropic agents, requires surgical intervention for ongoing bleeding, necessitates the transfusion of 4 or more units of blood (whole blood or packed RBCs) over a 48-hour period, or is a symptomatic intracranial hemorrhage (ICH)
PLATO	NSTE-ACS		• Combined major and life-threatening bleeding events defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g/dL or more, or the need for transfusion of at least 4 units of RBCs. Other major bleeding was defined as bleeding that led to clinically significant disability or bleeding either associated with a drop in the hemoglobin level of at least 3 g/dL but less than 5 g/dL or requiring transfusion of 2 to 3 units of RBCs **Minor bleeding** • Any bleeding requiring medical intervention but not meeting the criteria for major bleeding

NSTE-ACS, non-ST-elevation acute coronary syndromes; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction (see text for definition).

Adapted From Rao SV, Eikelboom JA, et al: Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1193-1204.

regimens uniquely define bleeding events among these trials. For instance in the CURE trial, Yusuf and colleagues[22] reported major bleeding as any life-threatening event resulting in hypotension or requiring more than 4 units of red blood cells (RBCs) and minor bleeding as any blood loss that led to the discontinuation of the study drug. The ACUITY trial investigators included access site bleeding requiring intervention, hematoma greater than 5 cm in diameter, and reoperation for treatment of bleeding in their trial-specific criteria for defining a major bleeding event.[21] Recent trials assessing the bleeding risks associated with novel, antiplatelet agents, prasugrel and ticagrelor have been completed. In assessment of prasugrel, The TRITON TIMI 38 trial utilized the previous TIMI bleeding risk scheme with additional life-threatening bleeding-event classification that was defined as a TIMI major bleeding event that is fatal, leads to hypotension requiring treatment with intravenous inotropic agents, requires surgical intervention for ongoing bleeding, necessitates the transfusion of four or more units of blood (whole blood or packed RBCs) over a 48-hour period, or is a symptomatic intracranial hemorrhage (ICH) (see Table 29-1).[34] Ticagrelor, a reversible inhibitor of the purinergic G protein–coupled P2Y 12 (P2Y12) receptor, was studied in the PLATO trial, which employed yet another ACS trial-specific bleeding

classification scheme (see Table 29-1).[35] The definition used in this trial was much more broad than in the TRITON TIMI 38 trial, and so led to higher reported rates of major bleeding. The incorporation of TIMI with GUSTO bleeding scales and existence of other trial-specific definitions of bleeding events precludes the ability to compare bleeding complication rates across ACS trials and to determine a single estimate of the incidence of bleeding complications among ACS patients.

Multiple treatment regimens have been assessed and approved for the management of ACS. Estimating the bleeding incidence is therefore confounded by the variability of pharmacologic therapies employed in the ACS literature. The addition of a novel, dual antiplatelet regimen (clopidogrel and aspirin) for the treatment of ACS in the CURE trial was associated with reductions in ischemic events (relative risk [RR] with clopidogrel as compared with placebo, 0.80; 95% confidence interval [CI], 0.72-0.90; $P < .001$), but at the expense of an increased risk for bleeding (3.7% in clopidogrel group vs. 2.7% in the placebo group; RR, 1.38; $P = .001$).[22] The ACUITY trial highlighted the importance of adding antithrombotic therapy to antiplatelet therapy as a component of the ACS management algorithm. The administration of bivalirudin alone compared with heparin plus a glycoprotein (GP) IIb/IIIa inhibitor for the ACS patient in the ACUITY trial was associated with reductions in major bleeding events at 30 days (3.0% vs. 5.7%; RR, 0.53; 95% CI, 0.43-0.65; $P < .001$) and demonstrated the non-inferiority of bivalirudin to heparin plus a GP IIb/IIIa inhibitor in relation to ischemic outcomes.

Another major issue is the variation in the use of invasive risk stratification across ACS trials. For example, the CURE trial included patients who were managed medically, as well as those who underwent percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). In contrast, the TRITON TIMI 38 trial was designed specifically as a trial that included patients undergoing PCI; very few patients underwent CABG or received medical therapy only. Similarly, the ACUITY trial included patients who underwent very rapid invasive risk stratification. The differences in the use of invasive procedures can have a large impact on bleeding risk and the subsequent reporting of bleeding events. Therefore, the applicability of the ACUITY, CURE and similar trials that have assessed the addition of novel, pharmacologic agents into the ACS management algorithm must be carefully considered.

Prognosis

Several studies describe an association between bleeding (regardless of definition) in the ACS population and adverse outcomes including death, stroke, myocardial infarction (MI) and unplanned revascularization (see Table 29-1).[9,10,20,21,27,31,36] For example, Moscucci and colleagues examined the GRACE registry of 24,045 patients with ACS (including UA, NSTEMI, and ST-segment elevation myocardial infarction [STEMI]) and found an association between GRACE major bleeding and increased in-hospital mortality.[27] Similarly, an analysis by Rao and colleagues,[9] examined 26,452 ACS patients enrolled in the PURSUIT, PARAGON B, and GUSTO IIb trials and demonstrated a stepwise increase in risk between bleeding severity and 30-day and 6-month death. Congruent with those studies, recent studies by Eikelboom and colleagues,[10] Manoukian and colleagues,[37] and Segev and colleagues,[31] describe a significant association between different definitions of major bleeding in ACS patients and adverse short-term and long-term outcomes including stroke and stent thrombosis.

Only one published study has directly compared the prognostic significance of different bleeding definitions. Rao and colleagues examined 15,898 patients from two clinical trials of ACS patients that used both the GUSTO and TIMI definitions of bleeding to classify the severity of bleeding complications.[9] When applied separately, each scale identified patients as having had a bleeding event that was missed by the other scale. Additionally, both GUSTO and TIMI bleeding were associated with an increased risk for 30-day death or MI when examined separately. When both definitions were included in the same model, increasing GUSTO bleeding severity was associated with a stepwise increase in the adjusted hazard of death or MI, whereas TIMI bleeding did not correlate with prognosis. Based on these data, bleeding defined by clinical events is likely more important in terms of prognosis rather than bleeding defined solely on the basis of reductions in hemoglobin concentration.[9]

One issue worth noting is the inclusion of blood transfusion as part of the bleeding definition in many studies. The administration of a transfusion is a discrete, documented clinical event that is easily captured. Data suggest that approximately 5% to 10% of ACS patients receive blood transfusions, and use of transfusions is higher in the United States than in other countries.[12,38] The "appropriate" use of blood transfusion administration is highly subjective due to lack of definitive data on transfusion triggers in patients with coronary artery disease[39]; therefore, transfusion may confound the bleeding–adverse outcomes relationship. Three large observational studies have found an association between transfusion and short-term mortality in patients with ACS.[11,12,40] Yang and colleagues analyzed data from 74,271 patients with ACS and found a significant association between blood transfusion and in-hospital mortality.[12] Wu and colleagues analyzed 78,974 elderly patients with acute MI and discovered that blood transfusion was associated with a significant increased risk of 30-day death among patients whose baseline hematocrit was greater than 33%.[40] Rao and colleagues examined 24,111 NSTE (non-ST-elevation) ACS patients and found that blood transfusion was associated with a significantly higher risk of 30-day mortality if the nadir hematocrit was greater than 24%.[11] The latter two studies highlight the controversy of defining a hematocrit threshold for administration of blood products in patients with ischemic heart disease. In practical terms, both studies underscore the concept that aggressive blood transfusion is associated with worse clinical outcomes. At issue is the inflection point at which the harm becomes manifest. Until further randomized data are available, it seems reasonable to transfuse ACS patients only if their hemoglobin is below 8 g/dL or their hematocrit is below 24% (in the absence of ongoing chest pain or active bleeding), per current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guideline recommendations. As antiquated practice guidelines supporting the liberal administration of blood products to ACS patients with a hematocrit of less than 24% may not be as benign as previously thought, it seems reasonable to conclude in addition, that routine use of transfusion to maintain arbitrary hemoglobin levels in asymptomatic patients should probably be avoided.

MECHANISMS OF BLEEDING AND INCREASED MORTALITY

Despite the strong association between bleeding and adverse ischemic events, the direct causality of bleeding complications and adverse ischemic events remains uncertain. Table 29-2 summarizes putative mechanisms that may explain the association between hemorrhagic complications and subsequent short- and long-term mortality and morbidity. Approximately 15% to 40% of ACS patients' hospitalizations are complicated by anemia.[41,42] Anemia, defined by the World

TABLE 29–2 Strategies to Minimize Bleeding Risk During Therapy for Acute Coronary Syndromes

Vascular Access Strategies	Pharmacologic Strategies
Radial artery approach Femoral head fluoroscopy prior to femoral arterial access	**Antiplatelet therapies** Lower aspirin dose (long-term) Wait 5-7 days after clopidogrel administration prior to bypass surgery. Wait 7 days after prasugrel administration prior to bypass surgery Avoid prasugrel in patients ≥75 years old, weighing <60 kg, or with prior stroke/transient ischemic attack Appropriate dosing of renally cleared glycoprotein IIb/IIIa inhibitors **Antithrombin therapies** Appropriate dosing of unfractionated heparin and low-molecular-weight heparins Use of fondaparinux in patients undergoing medical management Use of bivalirudin in patients undergoing PCI

Health Organization (WHO) as a hemoglobin of less than 13 g/dL, is an independent predictor of major adverse cardiovascular events and mortality in patients across the spectrum of ACS.[42,43] The pathophysiology underlying poor outcomes in anemic ACS patients may be explained by the combination of reduced oxygen delivery to the already hypoxic myocardium and the high myocardial oxygen demand secondary to the compensatory increases in heart rate and stroke volume.[44,45]

Normal, non-hypoxic myocardial tissue oxygen consumption and oxygen extraction are relatively constant at hemoglobins (Hgb) of greater than 7 g/dL. In the presence of coronary artery obstruction, however, ischemia has been documented with mild anemia (Hgb <10.0 g/dL).[46] Mild anemia reduces blood viscosity, decreases blood oxygen content and reduces afterload. Oxygen delivery to the hypoxic myocardium is normally augmented by a compensatory coronary vasodilatory response. Stenotic coronary vessels are devoid of the vasodilatory response and therefore compensatory increases in heart rate and myocardial contractility are employed to maintain systemic oxygen demands.

Bleeding may worsen myocardial ischemia in the ACS patient by inducing a mild anemia and state of tissue hypoperfusion. The subsequent, compensatory tachycardiac and upregulated myocardial contractility state result in a deleterious, myocardial oxygen supply and demand disparity.[42] Once bleeding results in anemia, the ACS patient continues to be at a dose-response risk for subsequent ischemic events. Bleeding events may also precipitate recurrent ischemic events by potentiating the inflammatory response through activation of the platelet and coagulation cascades.

ACS patients who experience major bleeding complications are subject to having antiplatelet and antithrombotic therapies discontinued. Spencer and coworkers[26] hypothesized that the premature cessation of these therapies provides a potential mechanism by which major bleeding is associated with increased ischemic outcomes in patients undergoing an ACS. Analyzing the GRACE database of ACS patients who suffered major bleeding (n = 506) within 2 days of admission, Spencer and colleagues compared this patient population to ACS patients who did not bleed during their hospitalization. Bleeding ACS patients were less likely to have received aspirin, thienopyridines, unfractionated heparin (UFH), or low–molecular-weight heparin (LMWH) after the first day of hospitalization. Appreciating the proven efficacy of these therapies for the prevention of recurrent ischemic events, withdrawal of these agents is expected to result in adverse outcomes. Importantly, mortality rates among ACS patients who experienced a major bleeding event were higher if aspirin (odds ratio [OR], 7.55; 95% CI, 4.43-12.88), thienopyridines (OR, 8.91; 95% CI, 4.39-18.12), and UFH (OR, 1.91; 95% CI, 1.09-3.36) were discontinued, compared with ACS patients who experienced a major bleeding event but continued therapy with these agents. These data are corroborated by an analysis of ACS patients enrolled in the PREMIER registry, which showed an association between in-hospital bleeding and lower use of aspirin and thienopyridine at discharge.[47] Patients who had experienced a major bleeding event were less likely to be restarted on dual antiplatelet therapy until 1 year after their initial hospitalization (Fig. 29-1). These data may explain the association between major bleeding and an increased risk for stent thrombosis.[48]

As noted, observational studies suggest an association between blood transfusion and adverse outcomes in the ACS population. Mechanistic studies have shown that transfusion of red cells paradoxically does not improve oxygen delivery. Stored blood is characterized by an increased affinity for oxygen because of decreased 2,3-DPG levels.[8,49] In addition, stored RBCs have alterations in their morphology and adhesion properties that many speculate increases the risk of vessel occlusion.[50-53] Nitric oxide (NO), the most potent vasodilator, is also depleted in stored RBCs.[54] Nitric oxide is essential for oxygen uptake into tissues.[55] The absence of NO leads to vasoconstriction, platelet aggregation, and ineffective oxygen delivery.[51] The synergistic effects of high oxygen affinity and ineffective oxygen delivery may account, in part, for the worse outcomes among transfused ACS patients.

PREVENTION

The development of increasingly efficacious antiplatelet and antithrombotic therapies and advancements in coronary

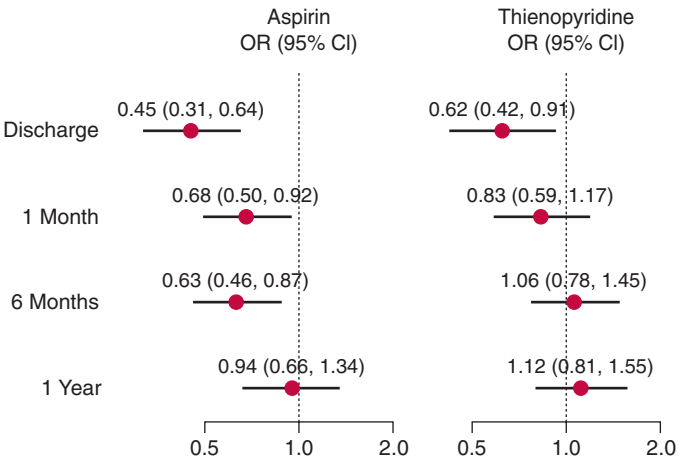

FIGURE 29–1 Association between in-hospital major bleeding and long-term adherence to aspirin and clopidogrel among patients with acute coronary syndromes. *(Adapted from Wang TY, Xiao L, Alexander KP, et al: Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139-2145).*

intervention have led to dramatic improvements in ischemic outcomes for the ACS patient. An optimal ACS management algorithm maximizes the anticoagulant benefit of pharmacologic agents, employs coronary intervention when indicated, while simultaneously minimizing the bleeding risks. Recent trials have correlated reductions in bleeding events with improvements in outcomes of death, MI, and stroke.[20,21,56] Reduction of bleeding complications has, therefore, become a priority in ACS management. Prior to the initiation of antithrombotic treatment, an assessment of bleeding risk should be obtained. Studies have consistently found that older age, female sex, lighter body weight, and renal insufficiency are associated with an increased risk for hemorrhagic complications.[13,27,37] Nikolsky and coworkers used data from the REPLACE-2 trial of urgent or elective PCI to develop a risk score,[57] but this score had poor discriminatory ability and it included treatment variables limiting its utility in guiding therapy. Subherwal and colleagues utilized the CRUSADE registry to develop a bleeding risk stratification tool that can provide an estimate of in-hospital bleeding risk based on baseline variables.[58] The tool is also available online (http://www.crusadebleedingscore.org) and may be helpful in targeting therapy, although this needs to be evaluated prospectively.

Established ACS management strategies associated with reduced bleeding risks are summarized in Table 29-2. These include alternative means of vascular access for coronary intervention, judicious dosing of antithrombotic therapies, and utilization of antithrombotic pharmacologic agents that are associated with lower bleeding risks. Aggressive anticoagulation and antiplatelet therapy, particularly with the use of GP IIb/IIIa inhibitors, has been shown to be associated with a risk of transfemoral access site complications of up to 10%.[36,59-61] Careful attention to femoral arteriotomy by using femoral head fluoroscopy can reduce access site complications.[62] An alternative is to use the radial artery approach for PCI, which is associated with a substantial reduction in bleeding and vascular complications.[63] Importantly, this reduction in complications appears to be consistent even when compared with a femoral arterial approach with vascular closure devices.[64] A recent meta-analysis of randomized trials that included more than 7000 patients demonstrated a strong association between the radial approach and decreased vascular complications.[65] These data are further supported by a study of more than 590,000 procedures in the National Cardiovascular Data Registry that showed an association between the radial approach and decreased bleeding or vascular complications without any compromise in procedure success.[66] Whether this reduction in bleeding is associated with improved survival is not known—one single center registry showed an association,[67] while a meta-analysis of randomized trials did not.[65]

In addition to vascular access, inappropriate administration and dosing of antithrombotic, antiplatelet, and GP IIb/IIIa inhibitor therapy has been implicated as a preventable cause of bleeding among ACS patients.[68] A recent review of medication administration from the CRUSADE registry of more than 140,000 ACS patients reported that 42% of patients received at least one excess dose of antithrombotic agent during their hospitalization.[69] Excess dosing of an antithrombotic agent was directly associated with increased rates of bleeding and prolonged length of hospital stay. Risk factors for receiving excessive doses of UFH, LMWH, or GP IIb/IIIa inhibitors included elderly, female, low body weight, diabetes, and heart failure. The authors report that 15% of major bleeding events in ACS patients are preventable with proper bleeding risk assessment and proper administration of anticoagulative agents. In women, excess dosing may account for up to 25% of the bleeding risk.[68] In this context, it is important to carefully adjust the doses of renally cleared agents, such as eptifibatide and LMWHs, in patients with renal insufficiency; dosing of intravenous UFH should be weight-based and apt values should be maintained in the range of 50 to 70 seconds.[70]

The administration of aspirin and clopidogrel to ACS patients is efficacious and supported by published guidelines.[70] However, the absolute increase in major bleeding is 1% higher with dual antiplatelet therapy compared with aspirin alone.[22] The risk of bleeding can be reduced by lowering the aspirin dose. In a post hoc analysis of 12,562 ACS patients enrolled in the CURE trial, Peters and colleagues[71] described an increased incidence in major bleeding directly associated with aspirin dose (aspirin alone: dose 100 mg, 1.9%; 101-199 mg, 2.8%; 200 mg, 3.7%; $P = .0001$; aspirin plus clopidogrel: dose 100 mg, 3.0%; 101-199 mg, 3.4%; 200 mg, 4.9%; $P = .0009$). There was no significant effect of aspirin dose on efficacy. Recently, the results of the CURRENT-OASIS 7 trial were presented.[72] This trial compared high-dose (600 mg, followed by 150 mg daily for 7 days) with standard dose (300 mg followed by 75 mg daily) clopidogrel and high-dose versus low-dose aspirin (300-325 mg daily vs. 75-100 mg daily). At 30 days, there was no difference in efficacy or safety between the high-dose and low-dose aspirin strategies. The effect of aspirin dose on safety after 30 days was not assessed in the CURRENT trial, and until further data are available, it seems reasonable to employ lower doses of aspirin 30 days after an ACS event in order to minimize bleeding risk.[73]

The major bleeding risk with clopidogrel use acutely is the risk associated with coronary artery bypass surgery. Because clopidogrel provides irreversible inhibition of the P2Y12 receptor, its antiplatelet effect is reversed only when new platelets are generated. Therefore, studies indicated an increased risk of surgical bleeding if CABG is undertaken within 5 days of clopidogrel therapy.[74] In order to minimize this risk, it is reasonable to wait 5 to 7 days after clopidogrel discontinuation before proceeding with bypass surgery; importantly, there does not appear to be a risk of increased ischemic events during this waiting period.[74]

Two other antiplatelet strategies deserve mention. Prasugrel, a thienopyridine that provides greater inhibition of platelet aggregation compared with clopidogrel, was evaluated in the TRITON TIMI 38 trial.[34] This trial demonstrated that a strategy of prasugrel plus aspirin reduced the combined incidence of stroke, MI, and death by 20% at 450 days of follow-up compared with a strategy of clopidogrel plus aspirin in ACS patients undergoing PCI. There was, however, a significant increase in TIMI major bleeding, including fatal bleeding. Three subgroups were identified in whom there was no benefit of prasugrel, but there was an increased risk of bleeding—patients older than 75 years, patients weighing less than 60 kg, and patients with prior stroke or transient ischemic attack (TIA). Ticagrelor, a reversible P2Y12 inhibitor, also provides greater platelet inhibition than clopidogrel. In the PLATO trial, ticagrelor plus aspirin was also more efficacious than clopidogrel plus aspirin in patients with ACS.[35] Despite this greater efficacy, there was no increase in overall major bleeding and a significant reduction in CABG-related bleeding. This is likely because of the reversible nature of the P2Y12 inhibition of ticagrelor. Importantly, there was an increase in non–CABG-related major bleeding among patients assigned to ticagrelor compared with those assigned clopidogrel, demonstrating that there is always a trade-off between greater potency of antithrombotic therapy and increased bleeding risk.

Recent trials of two anticoagulant agents, bivalirudin[75] and fondaparinux[20] have examined newer pharmacologic strategies to reduce bleeding. Bivalirudin is a specific and direct inhibitor of thrombin with a half-life of 25 minutes. It is

currently approved in the United States for the treatment of patients with unstable angina undergoing balloon angioplasty and for patients undergoing elective or urgent PCI.[76] The REPLACE-2 trial assigned 6010 patients undergoing urgent or elective PCI to receive UFH with planned GP IIb/IIIa inhibitor or bivalirudin with provisional use of a GP IIb/IIIa inhibitor administered for angiographic complications.[30] The composite, 30-day endpoint demonstrated no statistically significant difference in the primary quadruple endpoint of death, MI, target vessel revascularization, or major bleeding between study groups. This was driven by a statistically significant 40% relative risk reduction in major bleeding in patients assigned to bivalirudin. Although there was no significant difference in 12-month survival between arms, a trend toward lower 1-year mortality in the bivalirudin arm was appreciated. The authors speculated that this trend may be explained by the lower in-hospital bleeding rates. Whether these data are applicable to the population of patients with NSTE ACS was studied in the ACUITY trial.[75] ACUITY assigned 13,819 moderate-to-high-risk ACS patients to one of three treatment arms: heparin (UFH or enoxaparin) with GP IIb/IIIa inhibitor, bivalirudin with GP IIb/IIIa inhibitor, or bivalirudin alone (with provisional use of a GP IIb/IIIa inhibitor). The primary endpoint was net clinical benefit at 30 days that consisted of death, MI, ischemia-driven revascularization, or non-CABG major bleeding (defined differently from REPLACE-2). The bivalirudin-alone strategy was superior to the other two arms (heparin/enoxaparin plus GP IIb/IIIa: 11.7%; bivalirudin plus GP IIb/IIIa: 11.8%; bivalirudin alone: 10.1%; $P < .001$). Again, there were no significant differences in the rates of death, MI, or revascularization between the three arms, but there was a substantial reduction in ACUITY major bleeding among patients assigned to the bivalirudin alone strategy. One-year follow-up demonstrated no significant differences in mortality across the groups.[75]

Another agent that has been studied in the setting of ACS with a focus on bleeding reduction is fondaparinux. Fondaparinux is an indirect inhibitor of Factor Xa with a plasma half-life of 17 to 21 hours. The OASIS-5 trial randomized 20,078 ACS patients to receive fondaparinux or enoxaparin for 6 days.[20] The primary outcome of MI, refractory ischemia, or death at 9 days was not statistically different between study arms (5.8 vs. 5.7%; hazard ratio [HR], 1.01; 95% CI, 0.90-1.13). There was, however, a significantly lower rate of major bleeding (defined uniquely in this trial) at 9 days in patients treated with fondaparinux compared with enoxaparin (2.2 vs. 4.1%; HR, 0.52; 95% CI, 0.44-0.61). At 30-day follow-up, there was a statistically significant 17% reduction in 30-day mortality among patients treated with fondaparinux versus enoxaparin (2.9 vs. 3.5%; HR, 0.83; 95% CI, 0.71-0.97). The survival benefit associated with fondaparinux remained evident at the 180-day follow-up period. Patients who suffered bleeding (across both treatment arms) represented the majority of the mortality difference. OASIS-5 is the only trial to show that a strategy associated with reduction in bleeding risk also is associated with improved survival. There was, however, a hazard associated with the use of fondaparinux among patients who underwent PCI in OASIS-5. The incidence of catheter-related thrombus was higher among patients assigned to fondaparinux compared with those assigned to enoxaparin (1.3% vs. 0.2%), necessitating a protocol amendment that mandated the addition of UFH during PCI in patients treated with fondaparinux undergoing coronary intervention. The appropriate dose of UFH that should be added to fondaparinux to prevent catheter thrombus is unknown. Given this limitation, it seems reasonable that fondaparinux should not be the sole anticoagulant used in patients with ACS undergoing PCI.

CONCLUSIONS

Advances in the management of ACS over the past two decades have led to dramatic improvements in ischemic outcomes. However, this anti-ischemic benefit is associated with a concomitant increased risk for bleeding and blood transfusion. Variability in bleeding definitions across clinical trials makes it difficult to compare the risks of different therapies; however, it is evident that there is an association between bleeding and blood transfusion and an increased risk of adverse events including death, MI, and stroke. Given this relationship, and that evidence-based therapies are often discontinued in patients who develop bleeding complications, prevention of bleeding appears to be a prudent approach. Patients at high risk for bleeding complications, such as the elderly, females, and those with renal dysfunction should be identified as requiring strategies to minimize bleeding risk. When an invasive strategy is employed, consideration should be given to the use of the radial artery approach. In addition, careful dosing of antithrombotic and antiplatelet therapies is essential. Recently studied agents such as bivalirudin and fondaparinux have been shown to reduce ischemic complications while simultaneously reducing bleeding risk. In patients treated with clopidogrel prior to elective CABG, it is reasonable to wait 5 to 7 days before proceeding. For prasugrel, it is appropriate to avoid its use in patients older than 75 years, patients weighing less than 60 kg, and those with prior stroke or TIA, and imperative to delay surgery for more than 5 to 7 days. The bleeding risk with ticagrelor is modestly higher in patients treated medically, but it plays a significant role in minimizing bleeding risk in ACS patients requiring CABG.

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CHAPTER 30

The Patient with Disabling [Refractory] Angina Not Amenable to Revascularization Procedures

Udho Thadani

The number of patients with disabling angina who are not amenable to revascularization is growing progressively. A majority of these patients have undergone at least one coronary artery bypass procedure and percutaneous coronary interventions and are not suitable candidates for a further percutaneous coronary intervention or repeat coronary bypass surgery. Others have diffuse coronary artery disease or are at very high risk for a revascularization procedure because of comorbid conditions.

A patient with disabling angina not amenable to revascularization is one who remains symptomatic despite optimal medical treatment with beta blockers, calcium channel blockers, and regimens and formulations of long-acting nitrates that do not produce tolerance.[1-9] The following must be recognized, that in some patients: (1) triple therapy with beta blockers, calcium channel blockers, and nitrates may not be superior to treatment with two agents[10,11] and (2) adjustment of doses of a class of drug or changing to a different drug in the same class or withdrawal of a medication may help relieve anginal symptoms.[4,7,12,13]

It is also assumed that comorbid conditions such as anemia, thyrotoxicosis, arrhythmias, and other comorbid conditions that may aggravate angina and myocardial ischemia are absent or, if present, are adequately treated before disabling angina is diagnosed.

In addition to receiving antianginal drugs, all patients with disabling angina must abstain from smoking and should be treated with daily aspirin,[14] lipid-lowering agents (especially statins),[15,16] and angiotensin-converting enzyme (ACE) inhibitors.[17,18] These drugs are known to reduce serious adverse clinical outcomes in patients with coronary artery disease. Whether these agents decrease angina frequency or improve exercise tolerance in patients with disabling angina has not been adequately studied.

Patients with disabling angina experience angina with minimal activity or at rest. Many of these patients are hospitalized with unstable angina (UA) on multiple occasions, and at times it becomes difficult to evaluate if the pain is of ischemic, extracardiac, or mixed origin. In these circumstances, a perfusion scan obtained during an episode of chest pain can help the diagnosis.

Several therapies have been used or are recommended in addition to standard antianginal drugs, aspirin, statins, and ACE inhibitors to relieve angina and reduce adverse clinical outcomes. A multidisciplinary approach providing psychological support, positive feedback, treatment of depression, pain management by behavioral therapy, and cardiac rehabilitation has been successfully used in some European centers.[19] Trimetazidine, a metabolic modulator, has anti-ischemic effects and when added to standard antianginal medications may provide symptomatic relief in some patients.[20] The usefulness of newer antianginal drugs such as ranolazine, nicorandil, and ivabradine to treat patients with refractory angina remains to be proven. Noninvasive procedures, such as enhanced external counterpulsation (EECP) and transcutaneous nerve stimulation (TENS), and invasive procedures, such as spinal cord stimulation (SCS) and to a lesser extent transmyocardial laser revascularization (TMLR), are gaining popularity. Percutaneous transmyocardial laser revascularization (PTMLR) is ineffective. Gene and cell therapy, and other newer therapeutic modalities remain experimental. The use of many of these treatment modalities in patients with disabling angina is not based on well-designed placebo- or sham-controlled trials. The published data and expert options to treat these patients are discussed in this chapter.

OLD AND NEW DRUGS USED TO TREAT ANGINA

Bepridil

Bepridil, a nonspecific calcium channel blocker, exerts potent antianginal and

anti-ischemic effects.[3,6,7,21] A study showed that in patients with stable angina, a combination of bepridil and propranolol was superior to propranolol alone.[22] Bepridil was shown to be superior to diltiazem in another study.[23] Overall, published data suggest that bepridil increases exercise duration and reduces angina frequency more than other calcium channel blockers in patients with stable angina.[3,7] Unfortunately, bepridil prolongs the QT interval and can cause torsades de pointes in 1% to 2% of treated patients.[3,7] This is a major concern in patients with hypokalemia and in the presence of drugs that also prolong the QT interval.[3] There are no controlled trials with bepridil in patients with disabling angina who remain symptomatic despite maximal medical treatment and are not candidates for a revascularization procedure.[3] However, personal experience in several such patients suggests that bepridil is effective when other calcium channel blockers are not. Bepridil in place of other calcium channel blockers should be tried only in patients who remain symptomatic despite optimal medical treatment with beta blockers, other calcium channel blockers, and nitrates and those who are not candidates for revascularization.

Trimetazidine

Trimetazidine, a metabolic modulator, has anti-ischemic effects and improves exercise tolerance in patients with angina.[20,24-26] It does not have any significant effects on either heart rate or blood pressure and has been approved in many European and Asian countries for the treatment of angina. In experimental studies, it ameliorates myocardial ischemia by inhibition of oxidative phosphorylation and substrate utilization from free fatty acids to glucose.[27] Improvement in exercise tolerance and reduction in angina frequency has been reported when trimetazidine was added to standard antianginal drugs in patients with stable angina. Many of these patients had previous bypass surgery or percutaneous coronary revascularization procedure. However, from the published data it is unclear if the patients studied truly had refractory angina. Nevertheless, a trial of trimetazidine can be justified in patients with refractory angina. However, before its routine use, adequately powered placebo-controlled studies need to be carried out in patients with refractory angina.

Ranolazine

Ranolazine has been recently approved for the treatment of angina in the United States and some European countries. The exact mechanism of its action is unknown; it does block late sodium channel current and prevents cytosolic calcium accumulation in myocardial cells during periods of myocardial ischemia.[28] Either as monotherapy or when added to a beta blocker or a calcium channel blocker, or amlodipine with or without background treatment with a long-acting nitrate, it reduces angina frequency compared with a placebo.[29-31] It does not lower either the heart rate or blood pressure. The medication does prolong QT interval but its clinical significance remains unknown. In a large outcome trial in patients with acute coronary syndrome, ranolazine did not lower mortality or myocardial infarction rates compared with placebo, but it was safe and despite the prolongation of QT interval, it reduced the incidence of ventricular and atrial arrhythmias.[32,33] There are no studies of ranolazine in patients with refractory angina. However, many physicians including myself have used it as add-on treatment in patients with refractory angina; many of these patients have reported a reduction in their angina frequency. A placebo-controlled study is needed to evaluate the true usefulness of this medication in this group of patients with refractory angina.

Nicorandil

Nicorandil is a nicotinamide ester and a potassium channel opener and is currently being utilized in many European countries and Japan instead of long-acting nitrates for the treatment of stable angina and UA.[34] However, its antianginal effects have been questioned by some,[35,36] and its usefulness to treat patients with refractory angina remains to be proven.[37]

Ivabradine

Ivabradine by inhibiting I_f, an ion channel in the sinus node, lowers resting and exercise heart rate without exerting any other hemodynamic effects.[38] It exerts significant anti-ischemic and antianginal effects compared with placebo and the effects are comparable to those exerted by atenolol.[39-41] When added to atenolol, there was a further improvement in exercise duration and reduction in angina frequency in patients with stable angina.[42] In a large outcome trial in patients with ischemic heart failure, ivabradine did not reduce mortality but in a subgroup of patients with baseline heart rate above 76 beats/min, the drug reduced adverse clinical outcomes.[43,44] Its role in patients with refractory angina remains to be studied.

UNFRACTIONATED AND LOW-MOLECULAR-WEIGHT HEPARIN, ANTIPLATELET AGENTS, AND THROMBOLYTIC AGENTS

In patients with acute coronary syndrome, subcutaneous low–molecular-weight heparin (LMWH) plus aspirin reduces composite adverse clinical outcomes (death, myocardial infarction (MI), and refractory angina) compared with aspirin plus intravenous unfractionated heparin (UFH) especially in medically treated patients.[45,46] In patients with stable angina, however, intravenous UFH did not increase treadmill exercise duration.[47] Treatment with subcutaneous LMWH for several weeks increased exercise duration and exercise time to ischemia and reduced angina frequency in other studies.[48,49]

No placebo-controlled, double-blind trials have studied long-term treatment with either UFH or LMWH in patients with disabling angina.

Published results of the CURE trial[50] in patients with acute coronary syndrome (unstable angina or non-ST-segment elevation myocardial infarction [NSTEMI]) showed that treatment with clopidogrel plus aspirin for up to 11 months reduced the composite endpoint of death, MI, and stroke compared with placebo plus aspirin therapy. Prasugrel is a more potent antiplatelet agent compared with clopidogrel. In a large outcome trial in patients with acute coronary syndromes (ACS) who were treated with percutaneous coronary interventions (PCI), prasugrel plus aspirin reduced the composite endpoint of death, MI, and need for a repeat urgent revascularization compared with clopidogrel plus aspirin treatment in patients undergoing a percutaneous coronary intervention.[51] However, there was an increase in serious bleeding rates in the prasugrel group. The drug has been recently approved for clinical use in Europe and the United States for the treatment of patients with ACS who require PCI for the culprit coronary lesion, but with a black box warning of possible increase in serious and even fatal bleeding including hemorrhagic stroke. No data suggest that antiplatelet agents, including aspirin, clopidogrel, and prasugrel reduce angina frequency or improve exercise performance in patients with disabling angina. At present, data do not support the routine prolonged use of UFH or LMWH or antiplatelet agents (other than aspirin) to manage disabling angina.

In open trials with intermittent but prolonged administration of urokinase, relief of angina in patients with refractory angina was reported.[52,53] However, these studies were not placebo-controlled and, given the risks of increased bleeding with urokinase and other thrombolytics, these agents cannot be recommended to manage disabling angina.[54]

OTHER MEDICAL THERAPIES OF UNPROVEN VALUE

Chelation Therapy

Chelation therapy with ethylenediaminetetraacetic acid (EDTA) has been used to treat patients with peripheral vascular disease and those with known coronary artery disease.[54] However, placebo-controlled studies have failed to confirm that chelation therapy improves exercise performance in patients with intermittent claudication and those with stable angina pectoris.[55-57] No good published data suggest that chelation therapy is beneficial in patients with disabling angina.[54]

Enhanced External Counterpulsation

Enhanced external counterpulsation (EECP) mimics the principles of intra-aortic balloon pump counterpulsation in that EECP augments coronary blood flow in diastole and facilitates left-ventricular (LV) emptying in systole.[58-62] The EECP device currently marketed for clinical use consists of three paired pneumatic cuffs that are applied to the lower extremities.[62-66] The cuffs are sequentially inflated by applying 250 to 300 mm Hg of external pressure during diastole.[62] This increases venous return to the heart, with a resultant increase in cardiac output. An increase in aortic distention and pressure increases coronary blood flow in diastole.[62] The cuffs are deflated simultaneously in systole, reducing peripheral resistance to flow and thus providing LV unloading and easier emptying in systole.[62]

The EECP device has been in use for several years, but previous devices were cumbersome and difficult to use.[62] The newer device is operator-friendly and patient-friendly and has been approved by the Device Committee of the U.S. Food and Drug Administration (FDA) for clinical use. The approval has led to a wider use of the device in patients whose cases are considered refractory to conventional therapy and are poor candidates for revascularization procedures.[60,65,66] Whether such a practice is justified is open to question because of the lack of adequately designed studies in this group of patients.

Mechanism of Action of Enhanced External Counterpulsation

The exact mechanism by which EECP improves and maintains improvement in patients with stable angina remains unclear,[59,60,65] although various mechanisms—including an increase in collateral blood flow to the ischemic areas,[61] improvement in diastolic filling,[67] and neovascularization (angiogenesis) in the ischemic areas—have been proposed but not proven (Box 30-1).

Clinical Studies with Enhanced External Counterpulsation

Treatment requires 1-hour sessions, five times a week, for a total of 35 sessions[60,62,65]; and although EECP is noninvasive, it is expensive. Earlier studies with EECP, which were uncontrolled and used small numbers of patients, showed an improvement in stress perfusion imaging[61] associated with an increase in treadmill exercise duration compared with baseline and an improvement in exercise hemodynamics compared with pretreatment (Table 30-1).[67] In a single-center, open study of 50 patients, stress perfusion imaging improved after treatment in 75% of patients.[61] In one of the studies, the lowest response rate was noted in patients with the most extensive disease and the fewest proximally patent conduits, including both native coronary arteries and bypass grafts.[58,59] These uncontrolled studies also reported that patients treated with EECP continued to show an improvement in myocardial perfusion and angina frequency for up to 5 years.[64]

The only controlled study to evaluate EECP was the MUlticenter STudy of Enhanced External CounterPulsation (MUST-EECP).[62] Effects of active EECP treatment on exercise-induced electrocardiographic myocardial ischemia, total exercise duration, and anginal episodes were compared with sham EECP. Only patients with stable exertional angina with Canadian Cardiovascular Society (CCS) classes I to III were considered for the study. Patients were excluded for the following reasons: UA, a recent acute coronary syndrome, an MI or bypass surgery within the previous 3 months, a history of heart failure, a left-ventricular ejection fraction (LVEF) less than 30%, hypertension with blood pressure greater than 180/100 mm Hg, a history of phlebitis or severe peripheral vascular disease, warfarin therapy, atrial fibrillation, and frequent ventricular premature beats. A total of 500 patients were screened, of whom 139 were randomized. All

BOX 30-1 Enhanced External Counterpulsation (EECP)

Possible Mechanisms of Action

- Acute hemodynamic improvement mimicking the effects of intra-aortic balloon counterpulsation; increased coronary flow in diastole and improved systolic left-ventricular emptying and increased cardiac output (however, one would expect that the effects should last only during the treatment period of one hour each day)
- Increased collateral blood flow (unproven)
- Increased angiogenesis (unproven)
- Increased endothelial cell production of nitric oxide and prostacyclin (unproven)

TABLE 30–1 Clinical Studies with Enhanced External Counterpulsation (EECP) and Outcomes

Study Design*	Outcome
Open-label studies with baseline as control[58,61,62]	Increase in exercise duration Improvement in stress thallium perfusion imaging Reduction in angina Canadian Cardiovascular Class (CCC) functional class by 1 or 2 grades Lower response rate in patients with extensive disease and with poor conduits
MUST-EECP sham-controlled trial in stable angina[62]	No improvement in exercise duration Increase in exercise time to electrocardiographic myocardial ischemia (ST-segment depression) Reduction in angina frequency but not nitroglycerin consumption
Registry data with baseline as control in patients presumably refractory to conventional treatment[60,65]	Improvement in CCS functional class by 1 or 2 grades Local complication rate of 4% Safe in patients with heart failure

*Double-blind, sham-controlled studies in patients with disabling angina who are not candidates for a revascularization procedure have not been performed.

had evidence of electrocardiographic myocardial ischemia (ST-segment depression) during treadmill exercise in addition to exercise-induced angina. The ages ranged from 21 to 81 years. Patients received either active EECP with inflation pressures of 300 mm Hg or sham EECP with an inflation pressure of 75 mm Hg.

Of the 139 patients randomized, exercise data were available in only 115 patients. There were more patients in the active treatment group (n = 14) than the inactive treatment group (n = 4) who did not complete the study. The results failed to confirm that EECP improved total treadmill exercise duration.[62] Improvement in exercise duration was 42 plus or minus 11 seconds in the active EECP group and 26 plus or minus 12 seconds in the sham-EECP group ($P > .3$). However, time to stress-induced myocardial ischemia (1-mm ST-segment depression) increased significantly in the active treatment group compared with the sham-treated group (37 ± 11 seconds vs. –4 ± 12 seconds; $P = .01$), and there was also a decrease in angina frequency and improvement in functional class but no change in the sublingual nitroglycerin consumption in the active treatment group compared with the sham-treated group.

One of the drawbacks of the study regarding the evaluation of angina frequency was that patients were not asked to keep an anginal diary or an account of daily activities throughout the study. They were asked to remember whether they had any anginal attacks in the 24 hours preceding each treatment session.[62] More patients in the active EECP group experienced adverse events compared with the sham-treated EECP group (55% vs. 26%; $P < .001$). Device-related adverse experiences occurred in 33% of active EECP group members compared with 15% of sham-treated group members; paresthesias (2% vs. 1%), edema and swelling of legs (2% vs. 0%), skin abrasion, bruise, and blisters (13% vs. 2%), and pain in the back or legs (20% vs. 7%) were other findings in the active versus sham-EECP groups. The same investigators published a substudy in 71 patients on quality-of-life measures 12 months after treatment.[63] They reported a significant health-related quality-of-life improvement for up to 12 months after the completion of treatment with EECP.[63]

The EECP device was approved on the basis of this single trial in patients with stable angina. The approved indications included not only stable angina but also those with UA not responsive to conventional therapy. Subsequent to the approval of the device, registry data were prospectively collected.

The International EECP Patient Registry[65] reported the safety and benefit of EECP treatment in 548 patients with a history of heart failure.[66] At 6 months' follow-up, the procedure was well tolerated compared with patients without heart failure. However, significantly fewer patients with heart failure completed the course of EECP, and exacerbation of heart failure was more frequent, although angina class improved in 68% of patients with comparable quality-of-life benefit in the heart failure cohort.[66] At 6 months' follow-up, patients with congestive heart failure maintained their reduction in angina frequency but were significantly more likely to have experienced major adverse cardiac events (death, MI, and revascularization).

In a 1996 report of 2289 consecutive patients enrolled in an EECP consortium, EECP was found to be safe and well tolerated with a 4.0% rate of adverse experiences.[60] Angina class improved in 74% of patients with limiting angina (CCS functional class III to IV); patients who were most impaired at baseline demonstrated the greatest improvement, with 39.5% of patients in CCS classes III and IV improving two or more classes.[60] It is of interest that patients with CCS functional classes I and II, as well as III and IV, were included in the registry and that the results in the two groups were compared.

The registry data were updated (Fig. 30-1) and presented at the annual meeting of the American College of Cardiology in 2002 and showed marked improvement in functional class over time in the majority of patients. EECP's beneficial effects on psychosocial functions have been reported.[68]

International registry data confirmed the beneficial effects of EECP in 1458 patients with refractory angina.[69] Reduction in angina frequency following EECP therapy was still present at 2 years following the completion of a course of EECP compared with baseline angina frequency in 112 (8%) patients

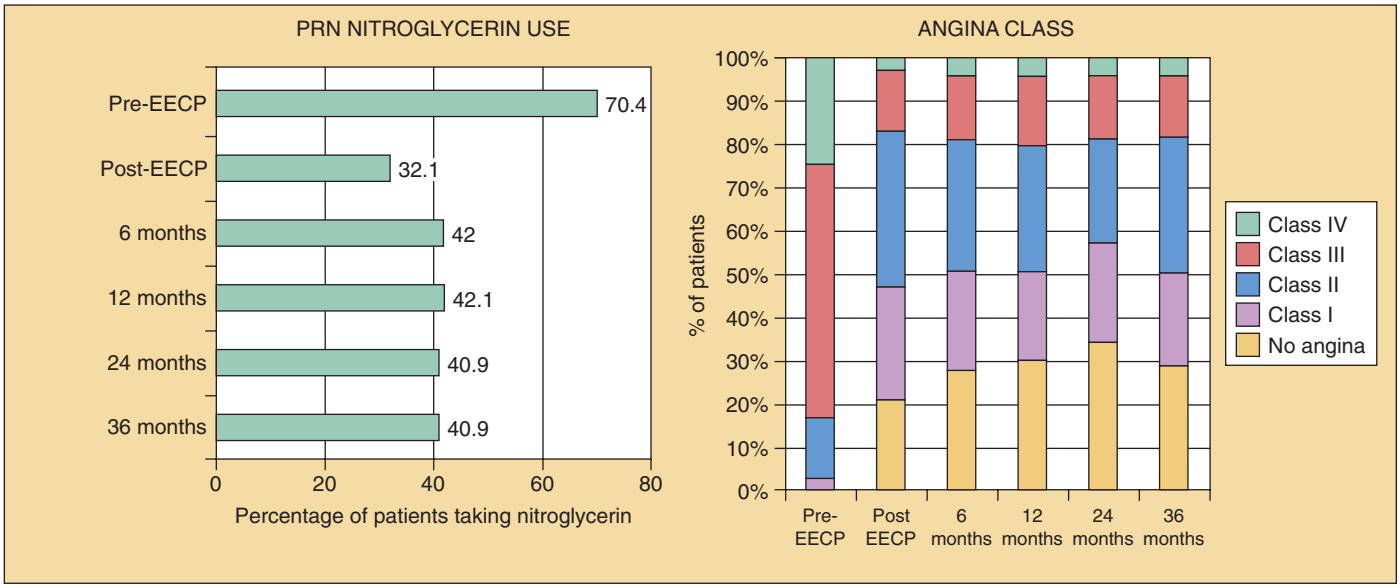

FIGURE 30–1 Changes in Canadian Cardiovascular Score (CCS) angina class and as-needed nitroglycerin use over time after enhanced external counterpulsation (EECP). Observational data before and 6 months, 12 months, 24 months, and 36 months after EECP therapy. Data reflect patients who completed the prescribed course of treatment and in whom follow-up information was available. From the International EECP Patient Registry (IEPR); database was frozen on 02/05/2002. *(From the IEPR Newsletter, March 2002; volume 4, issue 2).*

who had CCS angina class II at baseline (6.7 ± 10.2 vs. 2.4 ± 4.2 angina attacks per week) and in 1346 (92%) of patients with CCS class III and IV (12.2 ± 13.8 vs. 4.1 ± 8.7 angina attacks per week). It is surprising that despite refractory angina at baseline by 2 years, nearly 20% of patients underwent either a bypass procedure or percutaneous coronary intervention.

In another study in 86 consecutive patients with refractory angina and CCS angina class III and IV, 79% of patients experienced initial improvement and at 24 months 29% showed sustained improvement.[70]

It is unclear from the publications of the registry data whether all patients were on maximal medical treatment and whether they were candidates for revascularization. The reasons for treatment with EECP were diverse, including angina refractory to medical and surgical therapy, patient or physician preference, and poor candidates for surgery due to lack of graft material or targets or operative risk. During the study, only 0.2% of patients worsened by one CCS class.[65] The majority of the patients limited by their angina (CCS functional class II to IV) either improved their angina class (1531, or 73.4% of patients) or remained unchanged in functional class after EECP (554, or 26.5% of patients). Angina class improved by two or more functional classes in 48.5% of pretreatment angina class IV patients and in 34.9% of pretreatment functional class III patients. It is unclear whether any of the patients included in the registry had an ACS at the time of the study. In previous studies, patients with unstable and acute coronary syndrome were excluded.

Review of the published data leaves one to doubt whether the EECP treatment can be routinely recommended in patients with disabling angina who are not candidates for revascularization. No specific data have been published in this group of patients, and no controlled trials have been conducted. The only sham-controlled trial reported was in patients with stable angina, and that study failed to show an objective improvement in exercise tolerance, although there was an increase in time to ischemic threshold and a reduction in anginal episodes. Registry data are observational, not sham-controlled. Given a high rate of placebo response in patients with angina pectoris, it remains speculative whether EECP is effective in patients with disabling angina whose conditions are refractory to maximal medical therapy and who are not candidates for revascularization.

Thus, EECP treatment cannot be routinely recommended in patients with disabling angina whose conditions are refractory to maximum medical therapy and who are not candidates for revascularization. If the patient is very symptomatic, such therapy may be tried with the caveat that complete relief of angina or a reduction in anginal attacks might be a placebo effect during and after EECP. Such an approach may be justified if there are no other alternatives. However, before we accept routine EECP to treat patients with disabling angina who are not candidates for revascularization, adequately powered, sham-controlled studies need to be conducted to evaluate the effects of treatment on angina attacks, exercise tolerance, and the incidence of death and MI.

Neuromodulation (Spinal Cord Stimulation and Other Neurologically Based Therapies)

Several procedures have been used, some of which have been abandoned because of high complication rates.

Acupuncture

Acupuncture has been used to treat intractable pain including refractory angina.[71] Unfortunately, no sham-controlled studies have been published and the procedure is not widely used in the Western Hemisphere.

Thoracic Epidural Anesthesia

Anesthesiologists have used thoracic epidural anesthesia (TEDA) to control pain.[71] Although successful, the procedure produces only temporary relief of pain and requires repeated administration of the local anesthetic; thus, this modality is not widely used.

Stellate Ganglion Block

Temporary left stellate ganglion block relieves angina. Permanent destruction of the left ganglion with relief of refractory angina has been documented in case reports.[72] No controlled series have been published.

Transcutaneous Nerve Stimulation

For TENS, electrodes are applied to the chest, one in the dermatome with the highest intensity of projected or referred pain and the other in the contralateral dermatome.[73,74] The stimulus intensity is adjusted to just below the individual's pain threshold. TENS leads to high-frequency stimulation of large non-nociceptive myelinated type A fibers and inhibits the impulse through smaller, unmyelinated type C fibers, thereby reducing the activation of central pain receptors. Studies from Scandinavia show that TENS improved exercise performance and reduced electrocardiographic myocardial ischemia during exercise or pacing and reduced lactate production during pacing-induced ischemia.[73-78] Sympathetic discharge also was reduced.[76] No sham-controlled trials have been reported, although in a presentation at the American College of Cardiology in 2002, the lead investigator suggested a possible placebo effect.[75]

TENS units have been used successfully to treat refractory angina, and data suggest that this mode of therapy reduces myocardial ischemia and delays the onset of angina. However, the procedure is not widely used because of local skin complications of the device and the only support for using TENS to reduce angina frequency in patients with disabling angina has come from case reports.[77-81]

Spinal Cord Stimulation

Spinal cord stimulation (SCS) is primarily used in the Scandinavian countries, with few cases being performed in Europe, the United States, and other parts of the world.[82-95]

Procedure and Mechanism of Action. Low-voltage electric stimulation of the spinal cord inhibits the sensation of pain (Box 30-2). The sensation of stimuli is perceived as paresthesia. The dural space is opened, and an electrode is placed at the level of the T4 and T5 vertebra; a lead is placed at the T1 and T2 level.[83-85] During the procedure, the field of paresthesia produced is noted in the awake patient, and this should be in the area of referred pain. The stimulation device is connected to the lead and implanted under the skin in the abdomen or left lower thorax, and the patient is left with a small scar. The current applied varies from 2 to 7 volts, at rates of 30 to 90 Hz and a pulse width of 210 to 450 μJEK. The patient has a simple control mechanism and can turn the device on or off and can increase or decrease the amplitude of the current depending on the pain's intensity. The

BOX 30-2 Spinal Cord Stimulation (SCS)

Mechanism of Action

- Paresthesia in the area of referred pain
- Direct inhibition of sensory pathway carrying pain stimuli
- Reduction of myocardial ischemia
- Increase in pain threshold
- Reduction of sympathetic activity
- Reduction of myocardial oxygen demand

TABLE 30–2	Clinical Studies with Spinal Cord Stimulation (SCS)
Studies*	**Results**
Open trials[78-96]	Marked reduction in angina frequency, improvement in exercise tolerance
Holter monitor data compared with baseline data[89]	Reduction of ischemic episodes and angina frequency
SCS compared with coronary bypass surgery in patients with Canadian Cardiovascular Score (CCS) class III and IV angina[94]	Similar reduction of angina frequency Greater increase in maximum workload and reduction in exercise-induced ischemia with coronary bypass surgery Higher mortality in the coronary bypass group

*Double-blind sham-controlled studies in patients with disabling angina who are not candidates for a revascularization procedure have not been performed.

mechanism by which pain is alleviated is either direct inhibition of sensory pathways carrying the pain stimuli or a reduction of myocardial ischemia.[95]

Clinical Studies. Improvement in exercise duration and an increase in time to ST-segment depression and a reduction of total ischemic burden with SCS compared with controls has been well documented (Table 30-2).[83-86] Lactate production was also reduced during pacing-induced angina and SCS. Unfortunately, it is difficult to perform a placebo-controlled trial because the stimulation produces paresthesia. There has been a concern that abolition of pain with SCS may lead to myocardial ischemia not perceived by the patient and that a prolonged episode of silent ischemia might lead to MI. Studies under controlled pacing conditions show that the pain threshold is diminished but not abolished[91,95] and that higher pacing rates are required to produce angina.[91,95] Under conditions of exercise-induced increase in heart rate, the patient still perceives anginal pain despite SCS, though at a higher heart rate.[95]

Holter monitoring studies in 19 patients showed a marked reduction of ischemic episodes and relief of symptoms during SCS compared with pre-SCS baseline values.[89] No ventricular ectopy was induced by SCS.[89] Studies also have shown that SCS exerts antianginal effects and reduces myocardial oxygen demand. Myocardial ischemia is pacified but not abolished, and pain threshold is increased during SCS stimulation.[89,91,95]

In a recent trial in patients with stable angina pectoris and CCS class III and IV angina, 104 patients were either randomized to coronary bypass surgery or to SCS treatment. Relief of symptoms was experienced by 80% of patients in the coronary bypass surgery group and 84% of patients in the SCS group.[94] There was a marked reduction in angina frequency in both groups. There was a greater increase in maximum work performed in the surgical group than in the SCS group, and patients achieved a higher rate pressure product and had less ST-segment depression in the coronary artery bypass group.[94] Mortality in the coronary bypass surgical group was high compared with the SCS group (seven patients vs. one patient), with similar rates of nonfatal myocardial infarction (seven patients vs. seven patients).

In a retrospective analysis of patients treated with SCS,[91] 103 of the 517 patients had died by 23 months but had previously experienced a reduction in angina frequency. This was an observational study and not a controlled trial; therefore, results must be interpreted with caution.

In an open-label, single-center, randomized trial of spinal cord stimulation versus percutaneous myocardial revascularization (PTMR) in patients with refractory angina, there were no differences in main endpoint of exercise time or secondary endpoint of angina class between the two treatments.[96] This raises a question regarding the reported efficacy of SCS for the treatment of refractory angina as PTMR has been shown to be no more effective than a sham procedure.[97]

The following conclusions can be derived from the published data. The SCS procedure in experienced hands is safe and relieves angina. However, only a relatively small number of patients have been treated with SCS. There are no placebo-controlled trials, and it remains to be proven whether SCS is effective because of a marked placebo effect that has been documented in patients with angina. The reason for the infrequent use of SCS to treat refractory angina, according to a lead proponent of SCS, is that the procedure is performed by neurologists, whereas patients with disabling angina or no-option angina are treated by cardiologists, who do not receive any monetary gain for a procedure they do not perform themselves.

The reported safety of the procedure is reassuring, and SCS may be offered to patients with disabling angina despite maximal therapy who are not candidates for revascularization, even if the procedure were to produce a placebo-derived beneficial effect.

Sympathectomy

In patients with intractable angina, sympathectomy has been tried with success but the procedure is associated with significant morbidity and an increased mortality. For these reasons, the procedure has been essentially abandoned.[91,94]

Transmyocardial Laser Revascularization

The concept of creating transmyocardial channels to increase myocardial blood flow and oxygen supply goes back to an observation in reptiles, in whom a network of channels in the myocardium communicates directly with the ventricular cavity. In humans, there are no communications between the ventricular cavity and the myocardium. The concept to increase myocardial blood flow via ventriculocoronary anastomosis (sinusoidal network) was proposed by Wearn and colleagues in 1933.[98] Subsequently, successful channels were created by direct myocardial punctures in animals and with lasers in humans in 1986.[99]

Two types of laser devices have been used to create intramyocardial channels, the CO_2 laser and holmium:YAG laser. It has been claimed that more channels remain patent after the CO_2 laser device than after use of the holmium:YAG laser procedure, and the lesions created by the two procedures are histologically different.

Through a lateral thoracotomy, under direct vision but without cardioplegia or cardiopulmonary bypass, 10 to 50 (average, 24) laser channels are created in the left ventricle. The epicardial openings either close spontaneously or with light direct compression.

Mechanism of Action

It has been proposed that transmyocardial channels remain open after TMLR and may lead to angiogenesis (Box 30-3).[100] Unfortunately, many of the channels close soon after the procedure and there are few objective data to support increased angiogenesis.[101,102] One autopsy study showed microinfarcts in the areas around the TMLR channels, with evidence of local fibrosis and cardiac denervation.[102] The exact mechanism by which TMLR relieves angina remains speculative, although cardiac denervation remains a likely mechanism.[102,103]

Clinical Studies

Transmyocardial laser revascularization (TMLR) has been performed only in patients who are not candidates for

BOX 30-3 Transmyocardial Laser Revascularization

Proposed Mechanism of Action

- Exact mechanism unknown
- Increased blood flow to the myocardium via laser channels (most of the channels close spontaneously with time)
- Neovascularization (angiogenesis) (unproven)
- Cardiac denervation (likely)

TABLE 30–3 Clinical Trials with Transmyocardial Laser Revascularization (TMLR)

Trial*	Outcome
Open, uncontrolled reports	Improvement in anginal symptoms. Improvement in myocardial perfusion in >75% of patients.
CO_2 laser plus medical treatment vs. medical treatment[83]	No difference in exercise capacity or 12-minute walk test. Significant reduction in angina frequency. Periprocedural mortality (5%). No difference in mortality at 12 months.
CO_2 laser plus medical treatment vs. medical treatment[112,113]	Improvement in Canadian Cardiovascular Score (CCS) angina class and quality-of-life score. Improvement in thallium perfusion. Periprocedural mortality 3%. No difference in mortality at 12 months. High crossover rate in medical group.
CO_2 laser plus medical treatment vs. medical treatment[110]	Improvement in New York Heart Association (NYHA) angina class. Reduction in hospitalizations for unstable angina by 55% at 3-5 years follow-up. Increased incidence of heart failure; no difference in mortality or incidence of myocardial infarction at 3-5 years.
Holmium: YAG laser plus medical treatment	No difference in myocardial perfusion or ejection fraction or mortality at 12 months in treatment vs. medical treatment.[113] Significant increase in exercise duration and angina functional class.

*There are no sham-controlled trials with TMLR in patients with disabling angina who are not candidates for revascularization.

revascularization and have viable but ischemic myocardium. The procedure performed with CO_2 lasers and holmium:YAG lasers was approved by the Device Committee of the FDA for clinical use in nonoption patients (i.e., patients who are not candidates for revascularization or who are at very high risk because of comorbid conditions).

Initial open uncontrolled trials in patients with refractory angina reported significant improvement in anginal symptoms and myocardial perfusion on thallium imaging in more than 75% of patients over a 12-month follow-up period after TMLR compared with baseline observations (Table 30-3).[100,103-107] Uncontrolled open studies have confirmed these observations for up to 3 to 5 years of observations.[100,103-107] However, these studies were observational and not randomized or sham-controlled.[103] Improvement in myocardial perfusion reported in earlier studies is questionable because of lack of reproducibility during sequential studies.[108]

Schofield and coworkers compared TMLR with CO_2 laser plus continued medical treatment to medical treatment alone in 188 patients with CCS class III or IV angina.[109] Patients were randomly assigned to a treatment group. At 12 months, this study failed to show a statistical difference in exercise capacity or 12-minute walking distance between the two groups. The perioperative mortality rate was high in the TMLR group (5%), but the mortality at 12 months was similar in the two groups. Regarding subjective symptoms, there was a significant improvement in angina CCS functional class and a significant decrease in need for antianginal medications and fewer hospitalizations in the laser group. This trial failed to show an objective improvement in exercise duration, which was the primary endpoint of the study.[109]

In the Norwegian randomized trial, TMLR CO_2 laser plus optimal medical treatment was compared with optimal medical treatment in 100 patients with New York Heart Association class III and IV angina.[110,111] The angina class improved at 12 months,[110] an improvement still present at 3 to 5 years.[111] Hospitalizations for UA were reduced by 55% in the TMLR group after 3 to 5 years but not at 12 months.[111] Treatment for heart failure increased after TMLR, but there were no differences in mortality or the incidence of MI in the TMLR group compared with the medical group.[111]

Frazier and colleagues randomized 182 patients, with many patients in CCS angina functional class IV (69%), to either medical treatment plus TMLR CO_2 procedure or medical treatment.[112] At 12 months, there was a significant improvement in angina functional class, quality of life, and single-photon emission computed tomographic thallium imaging. There was also a marked reduction in rehospitalization for unstable angina in the TMLR group compared with the medical group (2% vs. 59%). However, survival rates at 12 months were similar. The perioperative mortality rate of the TMLR procedure was 3%. There was a high crossover rate to TMLR in the medically treated group.

In another study, TMLR plus continued medical treatment versus medical treatment alone in 275 patients with refractory angina showed a significant improvement in CCS angina functional class, a higher rate of cardiac event-free survival, a decrease in cardiac-related hospital admissions, and a higher rate of freedom from treatment failure.[113] In the TMLR plus continuous medical treatment group, despite an improvement in quality of life, myocardial perfusion did not differ between the two groups as assessed by thallium imaging. There was a high crossover rate from the medical group to TMLR therapy.

TMLR with holmium:YAG laser plus medical treatment was compared with medical treatment in 182 patients with CCS functional class III or IV angina.[114] There were no differences in myocardial perfusion or ejection fraction between the two groups as measured by echocardiography and dipyridamole thallium scanning. The mortality rates were also similar at 12 months. There was a significant increase in exercise duration and an improvement in angina functional class after TMLR therapy.

TMLR as a treatment option was approved after the TMLR procedure was documented to improve CCS angina functional class compared with medical therapy. No sham-controlled studies have been conducted.

Review of the published data with CO_2 or holmium:YAG TMLR shows conflicting results: Some studies show an improvement in myocardial perfusion and others show no improvement. Similarly, the effects of TMLR on exercise duration in different studies have shown either no improvement or a significant increase. The only consistent finding of all the studies has been an improvement in CCS angina functional class by one or two grades. None of the studies has shown a mortality benefit. The controversy has been discussed in several publications.[103,107-109] Perioperative morbidity and mortality of the procedure remain sources of major concern.[115]

Thus, caution is warranted in interpreting the data, especially in the absence of a placebo group. A high rate of symptomatic improvement and in functional class in patients with angina has been reported with placebo treatment in drug trials[7,19] and in a recent sham-controlled interventional trial with percutaneous TMLR.[116] The Vineberg procedure (implantation of the internal mammary artery directly into the myocardium) was in vogue in the early 1960s but was subsequently proven to be ineffective and abandoned. Thus, routine use of TMLR cannot be recommended in patients with refractory angina who are not candidates for revascularization because of the high initial perioperative morbidity and mortality related to TMLR.[103,114] Sham-controlled trials are needed to prove that TMLR is superior to continued medical therapy.

It has been argued that a sham-controlled study is unethical with TMLR because a thoracotomy is required and such a procedure will not be acceptable to the patient, the surgeon, or the FDA. Therefore, in patients who remain highly symptomatic despite maximal medical therapy, TMLR may be an option even if the response may be due to a placebo effect of the procedure because, in all of the published studies, angina CCS functional class has improved. However, it must be recognized that many of these refractory patients improve with time with continued optimal medical therapy.[117] A sham-controlled trial is therefore needed before TMLR can be accepted as a routine therapy in patients with disabling angina who are not candidates for revascularization.

Percutaneous Transmyocardial Laser Revascularization

Acceptance of TMLR to treat patients with no-option angina has led to a wider use of the device.[104-106] However, TMLR requires expertise and is associated with significant perioperative mortality and morbidity.[115] To avoid periprocedural complications, percutaneous catheters were designed, and it became feasible to perform laser myocardial revascularization via the retrograde femoral arterial approach, creating laser channels from the cavity of the left ventricle into the myocardium.[118]

Clinical Studies

Two early open-label studies showed encouraging results (Table 30-4).[118,119] In the Potential Angina Class Improvement from Intramyocardial Channels (PACIFIC) trial, 221 patients with CCS class III or IV angina that was refractory to medical treatment and not suitable for revascularization were randomized to PTMLR plus medical treatment or to medical treatment alone.[120] At 12 months, there was a significant increase in total exercise duration and an improvement in angina class score and quality of life, but the mortality was similar in the two groups. The incidence of myocardial infarction was not evaluated. In another study of 330 patients with CCS class II to IV refractory angina, medical treatment with PTMLR plus medical treatment led to an improvement in exercise tolerance and to improvement in angina class and quality of life.[120] Again, there was no difference in mortality in the two groups.

These trials were not sham-controlled. Given the known placebo effect in patients with angina, Leon and coworkers[116] conducted a sham-controlled study. In this double-blind randomized trial—the Direct myocardial revascularization In Regeneration of Endomyocardial Channel Trial (DIRECT)—298 patients were randomized to PTMLR with creation of 20 to 25 channels, a low PTMLR procedure with creation of 10 to 15 channels, or a sham (placebo) procedure with no laser channels created (Fig. 30-2). The trial was stopped prematurely at 6 months because there was a similar increase in treadmill exercise duration among the three groups. Furthermore, time to stress-induced electrocardiographic ischemia (1-mm ST-segment depression) and time to onset of angina were also similar among the three groups. There was a similar reduction in CCS angina class and improvement in quality-of-life indices in the three groups. The incidence of death and MI was also similar.

The results of this sham-controlled trial were completely divergent from the previously reported uncontrolled open trials and randomized trials that compared with medical treatment in that there was no objective or subjective improvement in the PTMLR group over the sham-treated group. The

TABLE 30–4 Trial Results of Percutaneous Transmyocardial Laser Revascularization (PTMLR)

Trials	Results
Open-label uncontrolled reports[117,118]	Reduction in angina frequency.
PTMLR plus medical treatment vs. medical treatment in Canadian Cardiovascular Score (CCS) angina class III and IV[119]	Significant increase in exercise duration and an improvement in angina CCS functional class and quality-of-life measurements at 12 months. Mortality similar in two groups.
PTMLR plus medical treatment vs. medical treatment in CCS class II-IV refractory angina[120]	Increase in exercise duration and improvement in angina functional class. No difference in mortality at 12 months.
PTMLR plus medical treatment vs. medical treatment in patients with refractory angina and occluded coronary arteries[121]	Similar improvements in functional class and exercise duration at 6 months. No differences in mortality or myocardial infarction rates.
PTMLR plus medical treatment vs. sham procedure plus medical treatment[115]	Trial stopped prematurely at 6 months; no difference in mortality, exercise duration, CCS angina functional class, quality-of-life indices, ischemic threshold, mortality, and myocardial infarction incidence.
PTMLR plus medical treatment vs. sham procedure plus medical treatment[122]	12-month study in 298 patients. No difference in mortality, exercise duration, CCS angina functional class, quality-of-life indices, ischemic threshold, mortality, and myocardial infarction incidence.

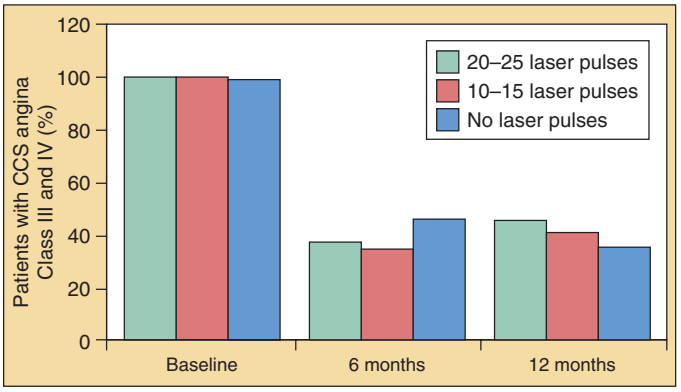

FIGURE 30–2 Effects of PTMLR compared to a Sham procedure on CCS angina class. There were reductions in CCS angina class in each treatment group but there were no differences between PTMLR and Sham groups. *(From Leon MB, Kornowski R, Down WE, et al: A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. JACC 2005;46:1812-1819.)*

DIRECT trial highlights the importance of a placebo-treated group to evaluate PTMLR or any other device or surgical procedure and clearly documents a marked placebo response even in very symptomatic patients with coronary artery disease.

In another randomized, single-blind trial, PTMLR with holmium:YAG laser plus maximum medical therapy (n = 71) was compared with maximum medical therapy (n = 70) in patients with refractory angina caused by one or more total coronary occlusions.[121] Percutaneous coronary intervention was attempted in all patients, but the procedure was unsuccessful in all the patients enrolled in the study. Patients were heavily sedated and did not know whether they were subsequently treated with PTMLR or not. At 6 months, angina class improved by two or more classes in 49% of patients treated with PTMLR and in 37% of those assigned to maximum medical therapy (P = .33). The median increase in exercise duration from baseline to 6 months was 64 seconds with PTMLR versus 52 seconds with maximum medical treatment (P = .73). There were no differences in 6-month rates of death (8.6% vs. 8.8%), myocardial infarction (4.3% vs. 2.9%) or any type of revascularization (4.3% vs. 5.3%) in the PTMLR and maximum medical therapy groups, respectively (P = NS for all). Another trial by Leon and colleagues failed to show improvement in exercise duration increasing quality of life as 12 months of PTMLR compared to sham procedure.[122] These observations confirm published data with drug trials in patients with stable angina, in whom an objective improvement in exercise performance and a marked reduction in angina frequency during placebo therapy has been consistently reported. PTMLR remains an investigative device and is not approved for clinical use by the FDA.

The results of the DIRECT trial[116,122] and a single-blind PTMLR trial[121] raise a major concern with the widely accepted results of the previously discussed TMLR procedure with CO_2 and holmium:YAG devices, which were not sham-controlled.[109-114]

A recent National Institute of Health and Clinical Excellent report from the United Kingdom concluded that percutaneous laser revascularization for refractory angina was ineffective and was associated with increased morbidity and posed unacceptable safety risks.[123] Therefore, this procedure should not be used.

Intra-aortic Balloon Pump Counterpulsation

Intra-aortic balloon pump counterpulsation (IABPCP) increases coronary blood flow in diastole and improves LV systolic emptying. The technique is effective in controlling angina and reducing myocardial ischemia in patients with refractory unstable angina. This mode of treatment is used as a bridge prior to coronary bypass surgery or during cardiac catheterization and PCI in hemodynamically compromised patients. However, the device increases the risk of local complications and limb ischemia with prolonged use.[124] There is no role for IABPCP in patients with disabling angina who are not candidates for revascularization because it may be difficult to wean a patient from IABPCP, which may result in serious local ischemic complications requiring local vascular surgery or even amputation of the leg.[124]

NEWER PROMISING BUT UNPROVEN TREATMENTS

Dietary Supplementation with Arginine

In a 2000 report[125] concerning patients with stable angina of CCS class II or III, a food bar enriched with D-arginine and a combination of other nutrients increased total exercise duration, improved quality of life, but had no effect on electrocardiographic manifestations of ischemia. Arginine also led to improvement in flow-mediated brachial-artery vasodilation. These observations confirm previous reports showing beneficial effects of L-arginine on exercise tolerance and endothelial function in patients with stable coronary artery disease.[126,127]

These observations are of interest; placebo-controlled trials in patients with disabling angina are needed to see if arginine and other nutrient supplements alleviate angina in this group.

Estrogen and Testosterone

Despite their documented vascular effects there are no studies that have evaluated the usefulness of these medications in patients with refractory angina. It is unlikely that these drugs will be evaluated, given the reported adverse effects during long-term therapy and a potential of an increase in cancer risk.

Angiogenic Gene Therapy

In patients with coronary artery disease, collateral blood vessels are often visible during angiography and these vessels open in response to chronic myocardial ischemia. However, collateral blood flow is inadequate in many patients with disabling angina, especially during period of increased myocardial oxygen demand. Stimulation of angiogenesis presents an attractive and additional or alternative approach for the treatment of coronary artery disease.[128] In animal models of myocardial ischemia, an increase in coronary collateral formation has been reported with continuous administration of agents into the left coronary artery and with intracoronary gene transfer of fibroblast growth factor (FGF) and adenovirus-mediated gene transfer of the complementary deoxyribonucleic acid and for vascular endothelial growth factor (VEGF).[129-131] Encouraging results were reported in phase I and pilot studies with VEGF and fibroblast growth factor (Table 30-5).[132-139]

Direct injection of FGF protein in the myocardium at the time of coronary bypass graft surgery resulted in angiographic evidence of enhanced collateral formation.[136,138]

In a randomized double-blind trial, low and high doses of recombinant VEGF, administered intravenously, were

TABLE 30–5 Trial Results of Angiogenic Gene and Cell Therapy

Trials	Results
Gene Therapy	
Direct injection of VEGF and fibroblast growth factors	Enhanced collateral formation; encouraging results in the myocardium.[136,138]
VEGF vs. placebo administered intravenously[139,143]	No differences in exercise duration.
PGF-2 vs. placebo[143]	No difference in exercise duration between the two groups. Subgroup analysis showed improvement in high- but not low-dose group; requires confirmation in adequately powered studies.
Open-label ad5-FGF4[144]	Beneficial effects on angina frequency.
ad5-FGF4 vs. placebo[144,145]	No increase in exercise duration or reduction in ischemic reversible defect size after ad5-FGF4.
Cell Therapy	
Cell therapy[147,148]	Initial studies look encouraging with reduction in MACE and reduction in CCS angina class and ischemic reversible perfusion defects.

compared with placebo in 178 patients with stable angina who were not suitable for revascularization.[139] At 60 days, there was an increase in exercise duration after VEGF and placebo, a primary endpoint of the study. Likewise, there were improvements in angina functional class, but no difference in myocardial perfusion after VEGF therapy compared with placebo. At 120 days, the angina functional class was better but no improvement in exercise duration could be detected after VEGF therapy compared with placebo.

In another study, different doses of a single intracoronary injection of FGF-2 were compared with placebo in a randomized double-blind study involving 337 patients.[140] At 90 days, there was an increase in exercise duration in both the active and the placebo groups, with no statistical difference between the FGF and placebo groups. This was the primary endpoint of the study. FGF-2 also did not improve myocardial perfusion. FGF-2 administration conferred an improvement in angina functional class at 90 days but not at 180 days.

These two double-blind, placebo-controlled trials failed to show beneficial effects of intravenous VEGF or of FGF-2 administered intravenously and in the coronary artery. These findings directly contrast with the beneficial results reported in open studies.[141-142]

In another study in 178 patients with refractory angina there was no overall benefit after 120 days following treatment with VEGF compared with placebo.[143] Subgroup analysis showed improvement in angina class in high-dose group but not the low-dose group compared with placebo. It remains to be seen if these results can be confirmed in adequately powered studies.

It has been suggested that gene therapy may be superior to protein therapy because the vascular endothelium or myocardium, or both, can incorporate genes, allowing sustained production of angiogenic protein. Open-label studies in humans have produced beneficial effects.[144] However, none of these studies was placebo-controlled.[144] In a 2001 report of 79 patients with coronary artery disease, safety and antiischemic effects of different doses of intracoronary human adenovirus-5 vector encoding human fibroblast growth factor 4 (ad5-FGF4) were assessed in patients with exercise-induced chronic stable angina of CCS class II or III.[144] The total exercise duration was increased by 1.3 minutes after gene therapy compared with an increase of 0.7 minutes with placebo (P = NS). The study was not powerful enough to evaluate the dose-response effects. Subgroup analysis showed a significant increase in exercise duration in patients with baseline exercise duration of 10 minutes or less. However, the significance of this finding remains questionable. Another trial with intracoronary ad5-FGF4 failed to show improvement in reversible perfusion defect compared with placebo in 52 patients with refractory angina.[145] The authors, however, reported a significant reduction in the ischemic defect size after ad5-FGF4 (4.2% < 0.001) and no improvement after placebo (1.6%, P = .32) compared with baseline values. The significance of these findings on a surrogate endpoint remains doubtful.

Large placebo-controlled studies with gene therapy are not available in patients with disabling angina who are not candidates for revascularization, and the results of ongoing studies in this group of patients are eagerly awaited. Concerns of increased atherosclerosis and the possibility of neoplasms secondary to gene therapy remain a concern.[130,142]

Thus, in the absence of adequately powered placebo-controlled studies involving patients with refractory angina, gene therapy remains experimental.

CELL THERAPY

In a phase 2 clinical trial, autologous CD34+ stem cells injected into the myocardium in patients with refractory angina were reported to be safe with a trend toward improvement in major adverse cardiac events (MACE) 25% versus 12.7% following low-dose and 14.3% with high-dose (P for trend .194). There was no reduction in angina episodes per week.[146]

In another trial in 26 patients, unselected autologous bone marrow mononuclear cells (ABMMC) transplanted by percutaneous retrograde sinus technique was reported to be safe.[147] Data were reported in only 12 of 26 patients. After a median follow-up of 21 days, the ABMMC transplantation led to significant relief of angina symptoms and improvement in functional class. This was associated with a significant reduction in ischemic myocardium by single photon emission computed tomography (SPECT) studies.

These and other studies raise the possibility that cell therapy may play a role in treating patients with refractory angina.[148-151] However, large randomized placebo-controlled studies are needed to establish this.

CORONARY SINUS REDUCER STENT

In a pilot study in 15 patients with refractory angina, coronary sinus reducer stent introduced percutaneously in the coronary sinus, improved CCS angina class at 3 year follow-up.[152] Sham-controlled studies are needed before accepting routine use of this procedure to treat patients with refractory angina.

EXERCISE TRAINING

Exercise training increases angina-free exercise duration in patients with stable angina.[153] Repeated exercise to angina is safe and may even reduce the incidence of serious adverse clinical outcomes compared with percutaneous coronary revascularization procedures in patients with stable angina.[154] It gives patients with refractory angina reassurance that it is safe to walk and exercise until the onset of angina. Exercise training has been shown to be safe and improves quality of life in patients with ischemic heart failure due to reduced LV systolic function.[155] Therefore, patients with refractory angina should be encouraged to take daily walks. Long-term effects of exercise training on symptoms and MACE, in patients with refractory angina, should be studied in adequately designed large-outcome trials.

OPIOIDS

In patients with severe disabling angina use of oral and transdermal opioids to relieve angina should be considered seriously to improve quality of life. A trial of epidural followed by intrathecal opioids might be beneficial. However, opioid dependence remains a major concern. A team approach for the evaluation of the risk-benefit and of the quality of life of chronic opioid therapy along with counseling is highly recommended as many of these patients may still live long.[123]

PERCUTANEOUS CORONARY INTERVENTION (STENTS) FOR TOTAL OCCLUSIONS

In the past, patients with refractory angina who had total chronic coronary occlusions (CTO) supplying an ischemic territory have not been considered to be suitable candidates for percutaneous coronary interventions. Coronary artery stents for CTO are not currently approved by the FDA. In

published series, stenting of CTO has been shown to be feasible and produces angina relief.[156] These results are encouraging but sham-controlled trials are needed before recommending this expensive procedure to treat patients with refractory angina who have CTOs considered to be responsible for myocardial ischemia and angina.

Percutaneous in Situ Coronary Venous Arterialization

Percutaneous in situ coronary venous arterialization (PICVA) redirects arterial blood flow from an occluded coronary artery to the adjacent vein, thereby arterializing the vein and providing retroperfusion to the ischemic myocardium.[157-159] An isolated report of PICVA in a patient with CCS class IV angina, in whom medical treatment had failed and who was not a good candidate for coronary bypass surgery or percutaneous intervention, resulted in complete relief of angina, increased perfusion to the ischemia area, and an increase in angina-free walking.[157]

Sham-controlled trials are needed before this procedure can be used to treat patients with disabling angina.

LAST-RESORT THERAPY

If all options fail and the patient continues to be disabled with angina, cardiac transplantation should be considered as an option provided there is no concomitant cerebrovascular disease or another comorbid condition that shortens survival. Long-term symptom-free survival is good in selected patients after transplantation. Donor hearts are scarce, and cardiac transplantation is usually offered only to younger patients with refractory angina who have no other comorbid conditions. Accelerated coronary atherosclerosis of the transplanted graft, however, remains a concern.

Best Available Options for Treating Disabling Angina

Increasing numbers of patients who are not candidates for revascularization are presenting with disabling angina.[160,161] One must optimize antianginal therapy and use aggressive lipid-lowering therapy in all such patients. Patients must be advised to stop smoking.

Many patients improve with optimal medical therapy. A trial of bepridil in selected patients instead of other calcium channel blockers is justified, provided there are no contraindications and the patient is made aware of the risk of possible torsades de pointes. Newer antianginal agents such as trimetazidine and ranolazine can be tried as add-on therapy for symptomatic relief; however, adequate studies with these agents in patients with refractory angina are lacking.[162]

No large placebo-controlled trials have studied EECP, SCS, or TMLR in patients with disabling angina. In placebo-controlled trials, PTMLR and VEGF and FGF-2 protein therapy were not superior to sham (placebo) therapy. This raises a major concern in accepting the results of TMLR trials, which were not sham-controlled. In symptomatic patients, EECP is a reasonable option even if the effects may be due in part to a placebo effect. SCS has more convincing documented physiologic effects and clinical benefit and should be considered as an option in patients with disabling angina. Cell-based therapy remains an exciting investigative approach.

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CHAPTER 31

Dietary Intervention in Coronary Care Units and in Secondary Prevention

Michel de Lorgeril and Patricia Salen

Secondary prevention of coronary heart disease (CHD) should be initiated promptly after the first clinical manifestation of CHD; in patients with an acute coronary syndrome (ACS), it is during the initial stay in the coronary care unit (CCU). In these patients, prevention should focus on the reduction of risk of recurrent cardiac events and death; the two main causes of cardiac death in these patients are sudden cardiac death (SCD) and chronic heart failure (CHF), often as a result of new coronary event. The main mechanism for such recurrent events is myocardial ischemia resulting from atherosclerotic plaque erosion or ulceration usually associated with inflammation in young lipid-rich plaques containing more saturated and unsaturated fatty acids than cholesterol (see Chapters 6 and 7).

These priorities in secondary prevention differ from that of primary prevention, where the main targets are traditional risk factors (e.g., smoking, dyslipidemia, diabetes, overweight or obesity, high blood pressure) and surrogate markers. These should be reinforced and their control more stringent after an ACS, while others are added, mainly prevention of malignant arrhythmias, SCD, and other morbidities associated with left ventricular dysfunction. SCD accounts for more than 50% of cardiac mortality in these patients,[1] is often unpredictable, and occurs largely out of hospital where therapeutic resources are most often not readily available.

This chapter covers these aspects of secondary prevention, focusing more on clinical outcome than on surrogate markers. Indeed, nutritional evaluation and personalized counseling are key to any prevention program as are exercise training, behavioral interventions such as support for smoking cessation, and drug therapy. The dietary prevention program is commonly initiated during hospitalization after a first CHD event; as hospital stays are getting shorter, the teaching takes place as soon as the patient is receptive within the first 48 hours and continued in cardiac prevention centers. Such programs are better developed under the guidance of a specialized dietitian and in close collaboration with the patient's cardiologist and primary care physician to assure consistency and continuity in care after hospital discharge.

A list of simple dietary recommendations to introduce in daily life will be provided at the end of the chapter for the many patients and families who find a formal and drastic re-education program difficult, recognizing that these recommendations will be minimal and not intended to replace a more global approach.

THE MEDITERRANEAN DIET: RATIONALE AND EVIDENCE FOR ITS BENEFIT

There is now some consensus to recommend the Mediterranean diet pattern for the secondary prevention of CHD, as no other dietary pattern was successfully tested so far in ACS patients. Contrasting with standard dietary approaches, which aim for a reduction of low-density-lipoprotein cholesterol (LDL-C) levels, the Mediterranean diet was shown to improve survival, mainly by reducing death from CHD and also from other various chronic diseases including cancers. Furthermore, the Mediterranean diet may be effective in reducing coronary atherosclerosis and the risk of fatal complications of atherosclerosis such as sudden death and congestive heart failure. Finally, unlike drug therapies, no harmful side effect has been reported using that dietary pattern.

Prospective epidemiologic studies on CHD have shown important differences in mortality rates across various populations that could pertain to differences in dietary habits.[2-4] Such is the case for relative protection against CHD and certain cancers in the Mediterranean populations that has been linked to dietary habits.[3,4]

The epidemiologic studies, however, only provide associations between risk factors and clinical end points, not causal relationships; the associations can be confounded by several factors including the economic situation and availability of extended social support systems. Clearly, randomized trials are the only way to make

sure that a given dietary pattern results in a significant protective effect against CHD complications.

Some dietary trials in primary or secondary prevention of CHD have reported significant reduction of CHD risk especially in terms of mortality[4-8] while others did not.[5] The successful trials in general tested dietary patterns characterized by a low intake of total, saturated and omega-6 polyunsaturated fats[6,7] and an increased intake of omega-3 fatty acids[6-8] without primarily aiming a reduction in blood cholesterol levels. Two of these trials[6,7] also included a high intake of fresh fruits and vegetables, legumes, and cereals containing large amounts of fiber, antioxidants, minerals, vegetable proteins, and vitamins of the B group. The credibility of these trials was considerably reinforced by a number of studies showing major protective effects of most of these foods and nutrients[8-17] with a particular emphasis on plant and marine omega-3 fatty acids.[6-9]

The Lyon Diet Heart Study was a randomized single-blind secondary prevention trial aimed at testing whether an experimental Mediterranean diet could reduce the risk of recurrence of an ischemia outcome event after a first myocardial infarction. It showed a significant reduction in the rates of cardiovascular complications.[7,18,19,20] Additionally, the trial suggested that the diet also protected from cancer.[21] Although further trials are warranted to confirm the cancer data, they are in line with several studies suggesting that dietary factors are important in cancers and cancer prevention.[22-28]

A recent and large observational study in a U.S. population provided strong evidence for a beneficial effect of good adherence to a Mediterranean dietary pattern on risk of all-cause mortality, including cardiovascular and cancer deaths.[29] They back their conclusions on previous non-U.S. epidemiologic studies reporting similar mortality data with the Mediterranean diet.[30,31] In another study of 74,886 U.S. women followed for about 20 years, a greater adherence to the Mediterranean diet was associated with a lower risk of CHD complications and stroke.[32]

These epidemiologic studies[29-32] consistently confirm the results of the Lyon Diet Heart Study.[33] Of interest, the Lyon Heart Study, showed no difference between groups in the main conventional risk factors, including blood cholesterol and blood pressure, suggesting that its protective effect is largely independent from conventional factors.

The diet scores that are used to assess conformity with the Mediterranean dietary pattern in the various epidemiologic studies[29-32] are generally nonperforming and do not capture the various practical aspects of the traditional Mediterranean diets. Clinicians and patients should know some fundamentals of the Mediterranean diet are:

1. A high variety of raw, sometimes cooked, seasonal vegetables year-round, often associated with large amounts of onions, garlic, parsley, rosemary, oregano, thyme and other aromatic herbs.
2. Fruit year-round, both fresh and dried (during the summer, for consumption in winter, e.g., apricots and grapes).
3. Various nuts (almonds, hazelnuts), particularly walnuts that are rich in alpha-linolenic acid (ALA), the main plant omega-3 and a major characteristic of traditional Mediterranean diets.[4] There are many other sources of ALA in Mediterranean diets, including many types of salads such as purslane[34] and products from animals fed with ALA-rich feed such as linseed (rabbit, eggs and chicken, dairy products).
4. Grains, preferably whole, especially wheat under the form of bread, fermented with natural leaven and sometimes flavored with ALA-rich linseed. The wheat used in traditional Mediterranean diets (like the vegetables and fruit) does not contain pesticides as they are not products of industrial agriculture.
5. Fatty fish, including anchovy, sardine, mackerel, sea bream and red tuna, all rich in very-long chain (marine) omega-3 fatty acids. Another source of indispensable marine omega-3 fatty acids are eggs of linseed-fed chicken, and possibly moderate wine drinking for an effect similar to fish eating.[35]
6. Olive oil, the main edible oil used around the Mediterranean area, low-saturated and rich-monounsaturated. However, the monounsaturated fat-saturated fat ratio used by the epidemiologists does not capture one major lipid characteristic of the Mediterranean diet, which is actually low in omega-6 and rich in omega-3 fatty acids. The omega-6/omega-3 ratio has been proposed as a major component of a healthy diet.[36]
7. In contradiction with many experts, Mediterranean populations do traditionally eat dairy products, though made of goat and ewe milk and not cow milk. Importantly, these are consumed as the fermented forms of cheese and yogurt, and almost never as milk, butter, or cream.
8. Mediterranean populations are not vegetarian. They eat ALA-rich eggs and small amounts of meat, mainly lean meat such as rabbit, chicken, and duck. Beef or pork, or both, are also on the menu in the North of the area, while lamb is the preferred meat for festive meals in the South. It is also important to note that everywhere in the Mediterranean area the diet includes a lot of legumes and is therefore rich in vegetable proteins.
9. Moderate alcohol drinking, essentially during meals, is a major characteristic of the Mediterranean diet. The main alcoholic beverage is wine, particularly red wine, a major source of various polyphenols (actually wine is a mix of ethanol and polyphenols). South of the Mediterranean Sea, the main source of healthy polyphenols is not wine but fermented black tea (a mix of water and polyphenols). Thus most people living in the Mediterranean area are high consumers of various polyphenols whose health effects[37] are still likely considerably underestimated by scientists and physicians; these have not yet been included in diet scores used by epidemiologists.

Questions arise on how effective is moderate drinking and on what cardiologists should tell their patients at risk of death.

The medical and scientific literature shows that moderate drinking (1-2 drinks/day for women and 2-4 drinks/day for men) is usually associated with a better life expectancy in the general population as well as in patients with established CHD.[38-41] In the absence of a controlled trial, which is neither technically nor ethically feasible, the main question for physicians remains whether the inverse association between moderate drinking and CHD complications is a cause-effect relationship. Some consider that most studies reporting alcohol-related protection carry bias, the main one retained being the "sick quitter bias," suggesting that non-drinkers (the referent group in most studies) include drinkers who recently quit because of an illness, resulting in a higher risk in so-called non-drinkers as compared to moderate drinkers. Previous prospective studies on light drinkers (rather than non-drinkers) as the referent group did not support such bias, and a recent study considering former drinkers and long-term abstainers separately, confirmed a true protective effect of moderate drinking compared with long-term abstainers.[41] Limitations of this study included a small sample size, few former drinkers and few cardiac deaths, and a short follow-up resulting in less protective effect than in other populations and meta-analyses that showed with moderate drinking with 30% reduction in cardiac mortality and 20% reduction of all-cause mortality.[38] Altogether these data strongly support a cause-effect relationship between moderate alcohol

drinking and better survival. These figures are considerable in terms of public health and compare with those observed with preventive drug therapy.

In the absence of clinical trials and definitive epidemiologic evidence, one can rely somewhat on biological plausibility. Beside the well-known effects of alcohol on high-density-lipoprotein (HDL) cholesterol, hemostasis (through reduced platelet function and fibrinogen levels) and insulin resistance, recent data indicate that moderate drinking may have a direct protective effect on the ischemic myocardium,[42] and positively interact with omega-3 fatty acids[35] known to be highly protective in secondary prevention, especially against SCD.[9]

Thus, cardiologists caring for high-risk post-acute myocardial infarction (AMI) patients should consider moderate alcohol drinking with a level of evidence similar to other measures to prevent sudden death, such as smoking abstention, regular physical exercise, a Mediterranean diet (of which wine drinking is one of the major characteristics), prophylactic drug therapy, revascularization procedures, and defibrillator (implantable cardioverter defibrillator) in candidate patients. Alcohol drinking may be as effective for this purpose as aggressive cholesterol lowering,[38-41] since the effects of statins on SCD are not clearly documented.

Wine drinking and statins have different pleiotropic effects with respective pathophysiologic significance that remains to be better understood. Alcohol acts on platelet function and coagulation to influence thrombosis, on leukocyte function to impact on inflammation processes, and on the incidence of malignant ventricular arrhythmia, pathophysiologic mechanisms that are all important in acute coronary syndromes and SCD.[43] The hazards of unsafe sex, violence, and accident representing the main alcohol-related morbidity and mortality among youngsters and among heavy drinkers, are much less of an issue in middle-aged or aging CHD patients. Finally, cardiologists should remember that moderate drinking is a social lubricant and a major characteristic of lifestyle, often associated with the feeling of "joie de vivre," notably in Southern Europe, the cradle of the Mediterranean diet.

The recommendations for approaching the patients are as follows: (1) to screen for heavy present or past drinkers to caution them that there is a way of drinking that can be beneficial for health and one that can be deleterious, and that abstention is better than abuse, (2) to identify the non-drinkers who abstain on the misconception that any alcohol drinking is bad for health, explain that moderate drinking, especially but not exclusively wine in the context of the traditional Mediterranean diet, is a most effective way to prevent both fatal and nonfatal complications of CHD.[39] This applies also in Northern Europe and in old age.[46] Further studies are needed to fully understand the mechanisms of that protection.

The answer to the issue as to whether wine drinking is superior to other alcoholic beverages for the prevention of atherosclerotic complications is not known, but observational data and meta-analysis suggest that wine may actually be more protective than beer and spirits.[47]

DIETARY PREVENTION OF SUDDEN CARDIAC DEATH

SCD is usually defined as death from a cardiac cause occurring within 1 hour from the onset of symptoms.[48] It is currently attributed to cardiac arrhythmia, although it is well recognized that classification based on clinical circumstances only is sometimes misleading. The magnitude of the problem is considerable, as SCD is a very common, often the first manifestation of CHD, and accounts for more than 50% of cardiovascular mortality in developed countries.[1,48] Most frequently, SCD occurs without prodromal symptoms and out of hospital. Because up to 80% of SCD patients suffer CHD,[49] the epidemiology and potential preventive approaches of SCD should theoretically parallel those of CHD. In other words, any treatment which targets a reduction of CHD is preventive of SCD.

Fish, n-3 Fatty Acids, and Sudden Cardiac Death

The hypothesis that eating fish may protect against SCD is derived from the results of a secondary prevention trial, the Diet And Reinfarction Trial (DART), which showed a significant 30% reduction in total and cardiovascular mortality in patients having at least two servings of fatty fish/week.[8] The authors suggested that the protective effect of fish might be explained by preventing ventricular fibrillation (VF), since the occurance of nonfatal was not influenced. This hypothesis was consistent with experimental evidence suggesting that n-3 polyunsaturated fatty acids (PUFA), the dominant fatty acids in fish oil and fatty fish, could prevant the occurrence of VF in the setting of myocardial ischemia and reperfusion in various animal models.[50,51] Using an elegant in vivo model of SCD in dogs, Billman and colleagues demonstrated a striking reduction of VF following the intravenous administration of pure n-3 PUFA, including both the long-chain fatty acids present in fish oil and alpha-linolenic acid, their parent n-3 PUFA found in some vegetable oils.[52] The authors explained this protection to the electrophysiologic effects of free n-3 PUFA that partitioned into the phospholipids of the sarcolemma without covalently bonding any constituents of the cell membrane. These fatty acids when ingested are preferentially incorporated into membrane phospholipids.[53] Nair and colleagues also showed that a very important pool of free non-esterified fatty acids localize in the normal myocardium, and that the amount of n-3 PUFA is increased by an n-3 PUFA-supplemented diet.[53] Ischemia promptly releases phospholipases and lipases that promote the release of new fatty acids from phospholipids, including predominantly n-3 fatty acids[53] that further increase the pool of antiarrhythmic free n-3 fatty acids. It is important to remember that the lipoprotein lipase is particularly active following the consumption of n-3 PUFA.[54] A hypothesis to explain these antiarrhythmic effects is a modulation of several membrane ion channels during ischemia,[55] including inhibitory effects on the fast sodium current, INa,[56] and the L-type calcium current, ICaL.[57]

Recent trials conducted in patients with ICD at high risk of VF on an ischemic or nonischemic cardiomyopathy provided, however, conflicting efficacy data on the prevention of SCD.[58-60] The administration of omega-3 fatty acid in the diet is therefore recommended only in deficient patients,[61] and not routinely in all ICD patients.

Other potential mechanisms for a benefit n-3 PUFA in SCD is a competing role in the formation of eicosanoids which are the precursors to a broad array of structurally diverse and potent bioactive lipids (including eicosanoids, prostaglandins, and thromboxanes), which are thought to play a role in ischemia and reperfusion induced[62,63] a reduction in heart rate variability.[64,65] Clinical studies have provided conflicting result on the efficacy of n-3 PUFA in CHD.

In a population-based case-control study, Siscovick and coworkers looked at the use of n-3 PUFA among patients with primary cardiac arrest, compared to age- and sex-matched controls.[66] The data indicated that the intake of about 5 to 6 grams of n-3 PUFA per month (an amount provided by consuming fatty fish once or twice a week) was associated with a 50% reduction in the risk of cardiac arrest. The value of the data was reinforced by the measure of n-3 PUFA levels in the red blood cell membrane, and the results were consistent

with those of many but not with all cohort studies.[67,68] Most studies, however, did not report on specific endpoint of SCD.

In a large prospective study that included more than 20,000 participants with a follow-up extending to 11 years, Albert and coworkers examined the hypothesis that fish intake could have antiarrhythmic properties and prevent SCD.[13] In the study, the risk of SCD was 50% lower for men who consumed fish at least once a week than for those who had fish less than once a month. The consumption of fish was not related to non–sudden cardiac death, suggesting that the main protective effect of fish (or n-3 PUFA) could be related to an effect on arrhythmia. These results are consistent with those of DART[8] but differ from those of the Chicago Western Electric Study, in which there was a significant inverse association between fish consumption and non–sudden cardiac death, but not with SCD.[14] Several methodologic factors may explain the discrepancy between the two studies, one being the criteria to classify deaths in the latter study. Again these observations illustrate the limitations of observational studies and the need for randomized trials to provide clear demonstration of causal relationships.

The GISSI-Prevenzione trial addressed the issue of health benefits of foods rich in n-3 PUFA and of vitamin E supplement, among 11,324 patients who have survived an acute myocardial, patients survived for at least three months. All patients were advised to follow a Mediterranean type of diet and randomly assigned in a 2 × 2 factorial design trial to supplements of n-3 PUFA (0.8 g daily), vitamin E (300 mg daily), both or neither for 3.5 years. Secondary analyses included overall mortality, cardiovascular (CV) mortality, and SCD. Treatment with n-3 PUFA significantly lowered by 15% the risk of the primary end point composed of death, non-fatal AMI, or stroke. Overall mortality was reduced by 20%, CV mortality by 30%, SCD by 45%, the later accounted for most of the benefits seen in the primary composite end point. There was no differences across the treatment groups for nonfatal events, a result comparable to that of the DART study.[8] In summary, the randomized GISSI trial, previous controlled trials,[6-8] large-scale observational studies[13,66,67] and experimental data[50-53] all support an effect of n-3 PUFA to reduce SCD in patients with CHD. This protective effect of n-3 PUFA on SCD was greater in subgroups of patients more compliant to the Mediterranean diet,[9,38] suggesting a positive interaction between n-3 PUFA and some components of the Mediterranean diet not enriched in n-6 PUFA and low in saturated fats, but rich in plant oleic acid, various antioxidants and fibers, and moderate consumption of alcohol.[35]

More, recent trials conducted in patients with ICD and left ventricular dysfunction following AMI or structural heart disease failed, however, to show a benefit of fish oil supplements at dosages similar to those tested in GISSI-Prevenzione.[58-60] An explanation could be that patients enrolled these triats were not deficient in n-3 PUFA, which is a major risk factor for SCD. New studies are needed to investigate the real status of n-3 PUFA in these specific patients and the subgroups that can benefit.

In summary, existing evidence supports the theory that an intake of n-3 PUFA to an amount of approximately 1 g daily, either as supplements or by eating at least two large (about 200 g) servings of fatty fish/week, helps prevent SCD in secondary prevention. At present, there are no reasons to recommend intake exceeding 1 to 2 g of n-3 PUFA/day. The dosage to be recommended in high-risk patients and in secondary prevention of SCD warrants further investigation.

Saturated Fatty Acids, Oleic Acid, Trans Fatty Acids, and n-6 Fatty Acids

With regard to other dietary fatty acids, animal experiments clearly indicate that a diet rich in saturated fatty acids is associated with a high incidence of ischemia- and reperfusion-induced ventricular arrhythmia, whereas PUFA of either the n-6 or n-3 family reduce this risk.[50-52] Most, but not all large epidemiologic studies have shown consistent associations between the intake of saturated fatty acids and CHD mortality.[69] SCD was not, however, a recorded end point in most of these studies. A clear demonstration of a causal relationship between dietary saturated fatty acids and SCD would require the organization of a randomized trial, which would not be ethically acceptable. Thus, besides the effect of saturated fatty acids on blood cholesterol levels, the putative mechanism(s) by which saturated fats increase CHD mortality remain unclear. If experimental data, demonstrating a proarrhythmic effect of saturated fatty acids be confirmed in humans, the first treatment would be to drastically reduce the intake of saturated fats. This has been done in randomized dietary trials and, as expected, the rate of SCD decreased in the experimental groups.[5-7] The beneficial effect cannot, however, be entirely attributed to the reduction of saturated fats as other potentially antiarrhythmic dietary factors, including n-3 PUFA, were also modified in these trials.

In contrast with n-3 PUFA, few data have been published so far in humans regarding the effect of n-6 PUFA on the risk of SCD. Roberts and colleagues reported that the percentage content of linoleic acid (LA; the dominant n-6 PUFA in the diet) in adipose tissue (an indicator of long-term dietary intake) was inversely related to the risk of SCD,[70] suggesting that patients at risk of SCD may benefit from increasing their dietary intake of n-6 PUFA, in particular LA, as for n-3 PUFA, but with a lesser degree of efficacy in most experiments.[50-52] Additionally, diets enriched in n-6 PUFA by increasing the LA content render the lipoproteins more susceptible to oxidation,[71] which theoretically contrain-dicated considering the putative roled lipoprotein oxidation in the inflammatory process associated with atherosclerosis plaque rapture, and SCD.[75-78] In fact, most diets high in n-6 PUFA have failed to improve the overall prognosis of patients with CHD.[5] In the Los Angeles diet study, which was a mixed primary and secondary prevention trial, the substitution of saturated fat for n-6 PUFA, was associated with a reduction of SCD (18 vs. 27), but this benefit was offset by a higher total mortality rate particularly from cancer (85 vs. 71).[79] Such negative effects were not reported with n-3 PUFA. Thus, despite the beneficial effect of n-6 PUFA on lipoprotein levels, which could, in theory, reduce SCD in the long term by reducing the development of atherosclerosis, it seems preferable not to increase the consumption of n-6 PUFA beyond the amounts required to prevent deficiencies in the essential n-6 fatty acid, LA (approximately 4% to 6% of the total energy intake), amounts that are found in the current average Western diet. A good substitute for saturated fat, is vegetable monounsaturated fat (oleic acid). The Mediterranean diet pattern, thus the contains the optimal fatty acid combination to prevent SCD by taking profit of the antiarrhythmic, antioxidant, and hypolipidemic effects of foods.[4,80]

Finally, Roberts and colleagues reported no significant relationship between trans isomers of oleic and LA in adipose tissue and the risk of SCD,[81] whereas Lemaitre and colleagues found that cell membrane trans isomers of LA but not of oleic acid are associated with a large increase in the risk of primary cardiac arrest.[82]

Thus, although specific human data on the effect of saturated fatty acids on SCD are lacking, results of several trials show their intake should be reduced in the secondary prevention of CHD (at least to reduce platelet reactivity). Despite a possible beneficial effect on the risk of SCD, increasing consumption of n-6 PUFA should not be recommended in clinical practice for patients with established CHD. Diets including low intakes in saturated fatty acid (as well as trans isomers

of LA) and n-6 PUFA (but enough to provide the essential LA) and high in n-3 PUFA and oleic acid (Mediterranean diet pattern) appear to be the best option to prevent both SCD and nonfatal AMI recurrence.[4-7]

Alcohol and Sudden Cardiac Death

The question of the effect of alcohol on heart and vessel diseases has been the subject of discussion in recent years (see earlier discussion). The consensus is now that moderate alcohol drinking is associated with reduced cardiovascular mortality, although the exact mechanism or mechanisms by which alcohol is protective are still unclear. In contrast, chronic heavy drinking has been incriminated in the occurrence of atrial as well as ventricular arrhythmias in humans, an effect called "the holiday heart" because it is often associated with binge drinking by healthy people, specifically during the weekend. Studies in animals have shown varying and apparently contradictory effects of alcohol on cardiac rhythm and conduction, depending on the animal species, experimental model, and doses of alcohol. Given acutely to nonalcoholic animals, ethanol may even have antiarrhythmic properties. In humans, few studies have specifically investigated the effect of alcohol on SCD. The hyperadrenergic state resulting from binge drinking, as well as from withdrawal in alcoholics, seems to be the main mechanism by which alcohol induces arrhythmias in humans. In the British Regional Heart Study, the relative risk of SCD in heavy drinkers (>6 drinks/day) was twice as high as in occasional or light drinkers.[83] However, the effect of binge drinking on SCD was more evident in men with no pre-existing CHD than in those with established CHD. In contrast, in the Honolulu Heart Program,[84] the risk of SCD among healthy middle-aged men was positively related to blood pressure, serum cholesterol, smoking and left ventricular hypertrophy but inversely related to alcohol intake. The Physicians' Health Study, which was the one study that looked at the risk of SCD in nonalcoholic, moderate "social" drinkers apparently free of CHD, reported a decreased risk of SCD.[43] After controlling for multiple confounders, men who consumed 2 to 4 drinks/week or 5 to 6 drinks/week at baseline had a significantly reduced risk of SCD (by 60% to 80%) as compared with those who rarely or never consumed alcohol. Secondary analyses, one excluding the deaths that occurred within the first 4 years of follow-up to rule out the possibility that some abstainers did so because of early symptoms of heart diseases, and the other based on a new evaluation of alcohol intake after 7 years to minimize potential misclassifications at baseline,[43] basically confirmed the potential protective effect of moderate drinking on the risk of SCD. Despite limitations (the selected nature of the cohort, an exclusively male study group, no information on beverage type and drinking pattern), this study suggests that a significant part of the cardioprotective effect of moderate drinking pertains to the prevention of SCD. Further research should be directed at understanding the mechanism or mechanisms by which moderate alcohol drinking may prevent ventricular arrhythmias and SCD.

In practice, current state-of-the knowledge supports the recommendation to drink one or two drinks/day, preferably wine during the evening meal, and never before driving a car or undertaking hazardous work.

DIET AND THE RISK OF HEART FAILURE FOLLOWING ACUTE MYOCARDIAL INFARCTION

The prevalence of chronic heart failure (CHF), which represents a most common terminal event in cardiac diseases, has steadily increased in many countries despite (and probably because of) considerable progress made in the management of acute and chronic CHD, which is nowadays the main cause of CHF in most countries.[85] Most research effort on CHF focused on drug treatment, with little attention to nonpharmacologic management. Many unidentified factors may however, contribute to the rise in the prevalence of CHF and should be recognized and corrected when possible. Thus, CHF is now seen as a metabolic problem with endocrine and immunologic disturbances potentially contributing to the progression of the disease.[86,87]

Nutrition and Chronic Heart Failure

While it is well appreciated that a high sodium diet is detrimental by promoting volume overload, little is known about other aspects of diet in CHF in terms of both general nutrition and micronutrients such as vitamins and minerals. Whereas the diagnosis and treatment of CHF is of first concern, it is also important to recognize and correct the traditional CHD risk factors such as high blood pressure, diabetes, malnutrition, and specific micronutrients deficiences that can entertain the disease process.

The importance for health of micronutrients is now fully recognized. These could be direct antioxidants such as zinc, or components of the antioxidant enzymes superoxide dismutase or glutathione peroxidase.[88] It is now widely believed (but still not causally demonstrated) that diet-derived antioxidants could play a role in the development (and thus in the prevention) of CHF. For instance, clinical and experimental studies have suggested that CHF may be associated with increased free radical formation[89] and reduced antioxidant defenses[90] and that vitamin C can improve endothelial function in patients with CHF.[91] In a recent trial, investigators have shown improved quality of life and left ventricular function in CHF patients receiving several antioxidant nutrients.[92] Taken altogether, these data suggest, but do not prove, that antioxidant nutrients help prevent CHF in post-AMI patients.

While CHF can be caused by deficiency of micro- or macro-nutrients such as selenium, CHF per se is associated with symptoms that affect food intake such as tiredness, shortness of breath, and gastrointestinal complaints as nausea, loss of appetite, and early feeling of satiety. Drug therapy and excess urinary losses can do the same.

It has been shown that up to 50% of patients suffering from CHF are to some extent malnourished.[93] Loss of weight is frequent and due to a variety of debilitating causes such as a higher metabolic rate at rest, a shift to increased catabolism with insulin resistance due to anabolic steroids, and loss of muscle bulk due to inactivity.[94,95] Levels of tumor necrosis factor-α (TNF-α), also known as cachectin, is elevated in many patients with CHF,[86,95] contributing also to the weight loss. Interestingly, TNF-α levels correlate with markers of oxidative stress in the failing heart[96] suggesting a link between TNF-α and antioxidant defenses in CHF. Finally, cardiac cachexia becomes manifested as symptoms worsen[97] and is a major predictor of imminent death. The pathophysiologic mechanisms that lead to cachexia remains unclear and so far, no specific treatment exist apart the treatment of the basic illness and correction of the associated biological abnormalities.

Deficiency in Specific Micronutrients

The deficiency in specific micronutrients should be of concern for physicians, because it can cause CHF, or at least aggravate it. The real prevalence of these deficiencies among patients with CHF and postinfarction patients and whether specific treatment will improve prognosis remain unclear. Indeed, a combination of minor deficiencies may be harmful, especially in the elderly. Many believe that the current

evidence supports the conduct of a large-scale trial of dietary micronutrient supplementation in CHF.[98]

Some relevant human data in CHF are:

1. Low serum and high urinary zinc levels,[99] possibly as a result of diuretic use but no data on zinc supplementation in that context exist.
2. Whether the slight elevation in plasma copper and lower zinc compared with controls without differences in patients with CHF in dietary intake[90]; are contributors to development of CHF or simply markers of a chronic inflammation found in CHF[86,95] remains to be investigated.
3. Selenium deficiency documented etiologic as a factor in some nonischemic CHF syndromes, especially in low-selenium soil areas such as Eastern China and Western Africa.[100]
4. Selenium deficiency as risk factor for peripartum cardiomyopathy.
5. In Western countries, cases of congestive cardiomyopathy associated with low antioxidant nutrients (vitamins and trace elements) in malnourished human immunodeficiency virus (HIV)-infected patients and in subjects on chronic parenteral nutrition.[101]
6. In China, an endemic cardiomyopathy named Keshan disease apparently has direct consequence of selenium deficiency. The exact mechanisms for such failure with selenium deficiency are unknown; recent data suggest that selenium may be involved in skeletal and cardiac muscle deconditioning, and contribute to the symptoms of fatigue and low exercise tolerance associated with CHF.[90] Indeed, in the Keshan area, the levels of selenium correlate better with the severity of CHF symptoms than the severity of left ventricular dysfunction assessed by echocardiography. Furthermore, raising selenium levels of the residents in this area to the levels found in nonendemic areas resulted in a significant decline in mortality rates without, however, reducing the prevalence of latent cases as detected by echocardiography.[100] What we learned from the Keshan disease and other studies conducted elsewhere[90] is a mild deficiency in selenium may influence the clinical severity of the disease.

   These data are strong incentive to initiate studies testing the effects of natural antioxidants on the clinical severity of CHF. In the meantime, physicians could consider measuring selenium in patients with an exercise inability that is disproportionate to the severity of cardiac dysfunction.
7. Finally, low whole blood thiamine (vitamin B_1) levels have been documented in patients with CHF administered loop diuretics with alcohol abuse and in hospitalized elderly patients; thiamine supplementation significantly improved cardiac function and symptoms.[93]
8. The presence of a low-grade systemic inflammation response syndrome (SIRS) in heart failure manifested by elevated circulating levels of cytokines and cytokine receptors is also a possible connection between diet and heart failure.[86,95] Since various anti-cytokine and immunomodulating agents may improve heart function and the clinical functional class in patients with advanced CHF,[102,103] a potential for dietary interventions exists. In that regard, it has been shown that supplementation with n-3 fatty acids (either fish oil or vegetable oil rich in n-3 fatty acid) reduces cytokine production in healthy volunteers.[104,105] An inverse exponential relationship exists between leukocyte n-3 fatty acid content and cytokine production by these cells, most of the reduction being due to a reduction in eicosapentaenoic acid in cell membrane to less than 1%, which is easily achieved with moderate n-3 fatty acid supplementation.[105] Low-dose marine n-3 PUFA less than 1 g/day resulted and was associated with a marginally better prognosis in a recent randomized trial in CHF patients.[106] Further studies are warranted to test whether higher dosages may influence the clinical course of CHF through an anti-inflammatory effect.

DIET AND PLAQUE INFLAMMATION, EROSION, AND RUPTURE

For several decades, the primary and secondary prevention of CHD has focused on the reduction of the traditional risk factors of smoking, hypertension (HBP), and hypercholesterolemia, aiming to halt the progression of the disease and promoting atherosclerotic plaque regression. It has become clear that efficiency first means prevention of clinical events and complications such as SCD and CHF, and only second the slowing down of the atherosclerotic process and neutralization of plaque inflammation and erosion and rupture that precipitates thrombotic occlusion. Recent progress in the understanding of the cellular and biochemical pathogenesis of atherosclerosis suggests that prevention of inflammation and rupture (see Chapter 26).

Is Coronary Heart Disease an Inflammatory Disease?

Proinflammatory factors (including the free radicals produced by cigarette smoking), hyperhomocysteinemia, diabetes, peroxidized lipids, and high blood pressure contribute to injury of the vascular endothelium, altering its antiatherosclerotic and antithrombotic properties. The fundamental differences that exist between the unstable, lipid-rich and leukocyte-rich plaque and the stable, acellular lipid-poor fibrotic lesions for the propensity to rupture bears poor correlation with the severity of the lumen obstruction.

Previous work by Virchow, Ross,[107] Libby,[108] and ourselves emphasized the role of inflammation and leukocytes inpromoting ischemic acute events.[109] It is now well accepted that one of the main mechanisms underlying the sudden onset of acute CHD syndromes, is erosion and/or rupture of an atherosclerotic lesion,[75,76] which triggers thrombotic complications and considerably enhances the risk of malignant ventricular arrhythmias.[77,78] Leukocytes have also been implicated in the occurrence of ventricular arrhythmias in clinical and experimental settings,[110,111] and can contribute to myocardial damage during both ischemia and reperfusion.[110] Clinical and pathologic studies showed the importance of inflammatory cells and immune mediators in the occurrence of acute CHD events,[72,112] and prospective epidemiologic studies show a strong and consistent association between acute CHD and systemic inflammation markers.[113,114]

Inflammation and Atherosclerosis: Many Questions

Although oxidized lipoproteins and vascular inflammation are considered to play an important role in CHD,[115-118] no antioxidant and no anti-inflammatory treatments have been shown effective in randomized clinical trials.[119-122] The same observation exists with inflammation; despite the role of macrophages and activated lymphocytes in atherosclerotic lesions,[72] no anti-inflammatory drugs have been useful so far (see Chapter 25).

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are ineffective, and patients with arthritis treated with these drugs have more CHD complications than those not exposed to these drugs.[123] Potential explanations are a

predisposition to insulin resistance and metabolic syndromes created by glucocorticoids, which are major risk factors for CHD.[124] In patients with established CHD, high-dose dexamethasone-eluting stents do not reduce in-stent neointimal proliferation and restenosis, an experimental model of human accelerated coronary atherosclerosis.[125] NSAIDs can be deleterious by causing an imbalance between prostacyclin and thromboxane A_2 and other mechanisms as well.[126,127] All these data and the perfect homeostasis that fits most individuals is highly complex and intriguing in the pathogenesis of atherosclerosis and CHD complications with so many pathophysiologic mechanisms and interactions.[126] In this context, it is certainly relevant to question environmental factors including diet and the role of essential polyunsaturated fatty acids as mediators of inflammation in the development of CHD.

Inflammation, Atherosclerosis, and Essential Fatty Acids

All stages of the atherogenic process imply dynamic interactions between inflammatory cells, cytokines, and inflammatory eicosanoids within the arterial wall.[72,115,127] According to the most popular theory to date, the conventional risk factors of CHD, including oxidized low-density lipoproteins (oxLDL), smoking, high blood glucose, and HBP, are harmful by initiating and promoting within the arterial wall the inflammation reaction associated with the atherogenic process. The earliest cellular event that can be detected in atherosclerosis is endothelial dysfunction that promotes monocytes rolling and adhesion to endothelial cells, and migration into the subendothelial space to the endothelium. This inflammatory response is facilitated by leukocyte-derived adhesion molecules expressed on the surface of endothelial cells. This process is thought to be driven by proinflammatory cytokines, and chemo-attractant chemokines and cytokines. Oxidized LDLs are thought to promote the accumulation of monocytes-macrphages into the subendothelium and the formation of foam cells.[72] Foam cells are a hallmark of fatty streaks, the first (but still reversible) visible stage of atherosclerosis. A later stage of inflammation is characterized by fibrosis, a major feature of atherosclerosis[72] produced by the proliferation of smooth muscle cells that migrate in the subendothelium from the muscular layer of the artery under the influence of various mitogenic and growth factors, such as the platelet-derived growth factor.[72] Fibrosis is a repair process that contributes to irreversible sclerosis and coronary obstruction, but is not subject to thrombotic complications because fibrosis is, in theory, a stabilizing factor of the plaques.

Although the inflammation theory of atherosclerosis is well anchored,[72,115] it is partly speculative as it does not account for the failure of antioxidant and anti-inflammatory treatment[119,120] drugs to prevent CHD complications.[119] New refinements in the theory are therefore required.

Of growing interest now are the effects of dietary fatty acids on immune parameters and on inflammatory process. Long-chain omega-6 PUFAs LA and even more arachidonic acid (AA) are potent inhibitors of lymphocyte function[128,129] as are omega-3 PUFAs.[130,131] These effects could be mediated partly by antagonizing inflammatory substances.[132] Other nonessential dietary fatty acids, for instance the omega-9 family, can also be involved in the inflammation process.

Actually, omega-6 PUFAs are now seen as proinflammatory and omega-3 PUFAs as anti-inflammatory.[132] Arachidonic acid, the major omega-6 PUFA in inflammatory cells, is the dominant substrate for eicosanoid synthesis that produces the major proinflammatory mediators potentially involved in CHD.[72,127] Blocking the initial step of AA synthesis in platelets at the level of cyclooxygenase-1 (COX-1) enzyme system does result in inhibition of platelet function. Most, but not all studies have suggested, however, that low doses of aspirin are as effective as the higher anti-inflammatory doses to prevent CHD complications,[133] suggesting that the benefit derived pertains more to antithrombotic effects of the drug rather than anti-inflammatory effects.[134] Nevertheless, controversies still persist on the best doses of aspirin that reduce CHD complications. It could also be that the optimal doses differ between populations. Indeed, recent data suggest that low-dose aspirin is not of major benefit in primary prevention, and also in specific patients such as diabetic patients with an asymptomatic vascular disease and cardiac transplanted patients.[135,136]

The absence of a better efficacy of high doses of NSAIDs raises important questions on the inflammatory theory of atherosclerosis considering that platelets regulate a variety of inflammatory responses through their interaction with the endothelium beyond their role in hemostasis and thrombosis.[137] They link inflammation, thrombosis, and atherosclerosis, highlighting the concept of *atherothrombosis* where thrombus formation is a starting point for progression of the disease through organization of residual thrombi.[137] Apart from specific conditions such as accelerated coronary atherosclerosis after heart transplantation,[138,139] the availability of conclusive human data to support the *atherothrombotic theory* is somewhat limited.

A second question relates to the role of inflammatory eicosanoids (from any source) in vascular inflammation and CHD. Why do substances blocking AA metabolism and the production of inflammatory eicosanoids and exhibiting potent anti-inflammatory effects (such as NSAIDs) have no effects[121,122] on CHD complications?

A third crucial question is how meaningful is the metabolic competition between the different families of PUFAs (omega-6, omega-9, and omega-3) in the vascular and anti-inflammatory effect of NSAIDs. Could COX inhibition have the same clinical effect in patients with very different dietary intakes in omega-9, omega-6, and omega-3 fatty acids?

In view of the complexity of these questions, only certain aspects of the role of essential PUFAs in CHD through their pro- or anti-inflammatory properties will be discussed.

There are many recent reviews of the biology and metabolism of essential PUFAs.[140,141] Essential PUFAs are fatty acids that contain two or more double bonds; the nomenclature is based on the number of double bonds and the position of the first double bond counted from the methyl terminus of the acyl chain. Thus, an 18-carbon fatty acid with two double bonds in the acyl chain and with the first double bond on carbon number 6 from the methyl terminus is termed 18:2 omega-6 (or 18:2n-6). The common name of this fatty acid is linoleic acid (LA) and it is the simplest member of the omega-6 family of PUFAs. Linoleic acid can be further desaturated by insertion of a double bond between carbons 3 and 4 to yield alpha-linolenic acid (ALA; 18:3 omega-3 or 18:3n-3), the simplest member of the omega-3 family of fatty acids.[141] Plants, but not mammals, have the desaturase enzymes required to synthesize LA and ALA. For this reason, LA and ALA are said to be "essential," which means that they have to be supplied through our daily diet to cover our needs (Fig. 31-1). Plant seed oils (and margarine) from corn, sunflower, and soybean are the main sources of LA in the Western diet. Nuts, canola oil, and green leafy vegetables are the main sources of ALA in the Western and Mediterranean diets.[141] LA is the most important PUFA in the Western diet with an average intake between 12 and 20 g/day, and an LA to ALA ratio of 20 or 25 to 1 depending on the populations studied. The minimum intake of ALA for the prevention of cardiovascular disease (CVD) should be about 2 g/day and the preferred LA to ALA ratio of 4 or less.[141] In many countries,

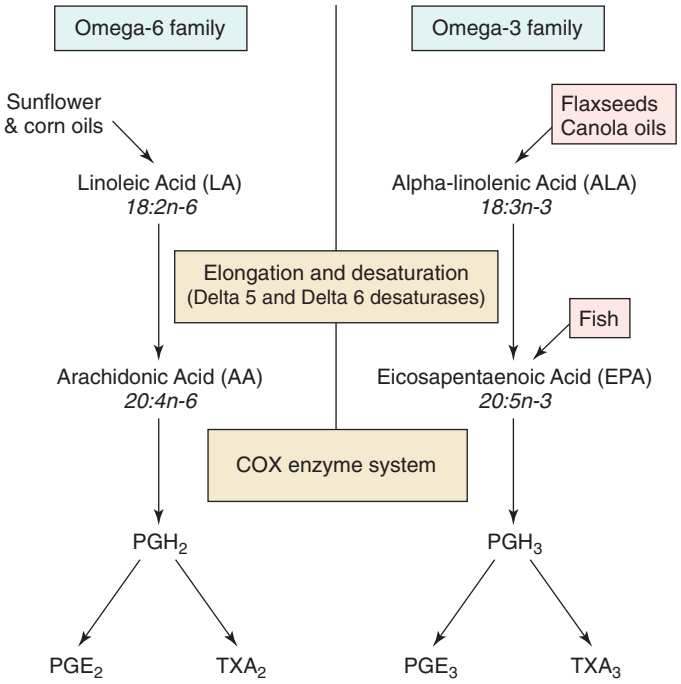

FIGURE 31-1 Schematic representation of the metabolism of 18-carbon fatty acids into longer chain fatty acids and subsequent eicosanoid metabolism under the effect of the COX system. Most AA in the body comes from LA (through endogenous biosynthesis), whereas most EPA comes from dietary intakes provided by fish. Eicosapentaenoic acid (EPA) can be further metabolized to produce DHA (see text). An alternative pathway for AA and EPA is the LOX system (see text).

however, the ALA intake is lower than 1 g/day. LA and ALA are the main PUFAs in the Western and Mediterranean diets and longer-chain PUFAs (with 20 carbons or more) are consumed in small amounts: from 50 mg (often) to 500 mg (rarely)/day for AA (20:4n-6) and for the long-chain omega-3 PUFAs mostly found in fish, eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). Mammals are in theory able to synthesize EPA and DHA from ALA.[141] In fact, in patients at high risk of CVD complications, a high ALA intake resulted in a significant increase in blood and tissue EPA levels, whereas the increase in DHA was low and not significant.[4,6,19] Thus, DHA is often considered *essential* like LA and ALA, and it is prudent to provide for minimum amounts of it at least 200 to 500 mg DHA/day, depending on the associated amounts of ALA and EPA present in our daily diet. Unlike ALA (the precursor of EPA), oleic acid (18:1n-9) is consumed in substantial amounts in the typical Western diet and is not an essential fatty acid. Oleic acid is the precursor of eicosatrienoic acid (ETA; 20:3n-9), the main omega-9 PUFA potentially involved in inflammation by competing with AA (and EPA) at the COX and LOX (lipoxygenase) levels. However, there is little ETA in cell membranes, probably because of the overwhelming competition from dietary LA and ALA for the relevant desaturase and elongase enzymes.[142] ETA is nonetheless assumed to decrease synthesis of leukotriene (LKT) B_4, a major inflammatory mediator, partly through a direct effect on $LKTA_4$ hydrolase (Fig. 31-2). ETA also is a substrate for 5-LOX and may compete with AA for the formation of $LKTA_4$, especially in case of severe LA restriction leading to elevated ETA concentrations.[142] It is noteworthy that the Mediterranean diet is poor in LA and rich in oleic acid, which is another context where ETA concentrations are relatively high compared with the LA-rich Western diet. Thus, whatever the nutritional context (severe LA restriction or Mediterranean diet), and in partial analogy to the situation with EPA, elevated ETA concentrations can also alter the balance of eicosanoids produced by leukocytes toward a potentially less inflammatory mixture.[142] The effect of ETA on COX is less clear than on 5-LOX although inhibition of endothelial (PGI_2) production has been ascribed to ETA.[143] This could, at least theoretically, increase the risk of thrombosis. Thus, a traditional Mediterranean diet with high intakes in oleic acid and omega-3 PUFAs, from both vegetable and marine sources, and low intakes in saturated fatty acids and LA may be the best compromise to reduce the risks of both inflammation and thrombosis. This has been confirmed in clinical trials.[7,19,144,145] In any case, as emphasized by several major investigators in the field, the background omega-6 PUFA content of the diet is a key issue when fortifying diets with either omega-9 and/or omega-3 fatty acids with a therapeutic or health-enhancing purpose.[132,141,142] A key link between PUFAs and inflammation relates to the fact that the family of inflammatory mediators termed eicosanoids is generated from 20-carbon PUFAs released by cell-membrane phospholipids (see Fig. 31-2). Inflammatory cells are thought to typically contain a high proportion of the omega-6 AA and low proportions of the omega-3 EPA. In fact, the AA to EPA ratio is extremely dependent on the dietary habits of the populations in question.[7,142,146] In persons following a typical Western diet (with a very high AA to EPA ratio), AA is the dominant substrate for eicosanoid synthesis. In contrast, in persons following a Mediterranean diet poor in omega-6 PUFAs (but rich in omega-9 oleic acid and omega-3 PUFAs), the relevance of AA and AA-derived eicosanoids is reduced. Eicosanoids include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LKTs), and many other less studied substances (see Fig. 31-2). AA is mobilized from cell membranes under the effects of phospholipases and subsequently acts as a substrate for the enzymes that synthesize eicosanoids. The metabolization of AA by COX gives rise to the 2-series PGs and TXs. However, when EPA is the substrate for COX instead of AA, the eicosanoids that are produced belong to the 3-series, the properties of which are very different (less inflammatory, less vasoconstrictive, less prothrombotic) from those of the 2-series.[132] Substances derived from ETA are less well characterized and their physiologic roles are not clearly determined.

There are two isoforms of COX: COX-1 is a constitutive enzyme and COX-2 is induced in inflammatory cells as a result of stimulation (for instance by cytokines produced by activated leukocytes) and accounts for the marked increase in eicosanoid production that occurs in activated cells. It is very important to understand that PGs are formed in a cell-specific manner (see Fig. 31-2). For instance, monocytes (and macrophages) produce large amounts of PGE_2 and PGF_2, neutrophils produce moderate amounts of PGE_2 and mast cells produce PGD_2. Arachidonic acid metabolization through the 5-LOX pathway gives rise to hydroxyl and hydroperoxyl derivatives and to the 4-series LKTs. Eicosapentaenoic acid (EPA) metabolization by the 5-LOX pathway gives rise to 5-series LKTs, which have a considerably lower inflammatory effect than 4-series LKTs.

One of the major inflammatory AA-derived 2-series PGs is PGE_2. Its proinflammatory effects include fever, increased vascular permeability and vasodilatation, as well as increased pain and edema. PGE_2 induces COX-2, upregulates its own production by leukocytes, and induces the production of inflammatory cytokines (TNF, interleukins), which are other major mediators of inflammation that are able to recruit new leukocytes and again induce COX-2. However, PGE_2 was also found to inhibit 5-LOX, decreasing the production of the 4-series LKTs, and to induce 15-LOX, promoting the formation of lipoxins.[147] The latter mediators have potent

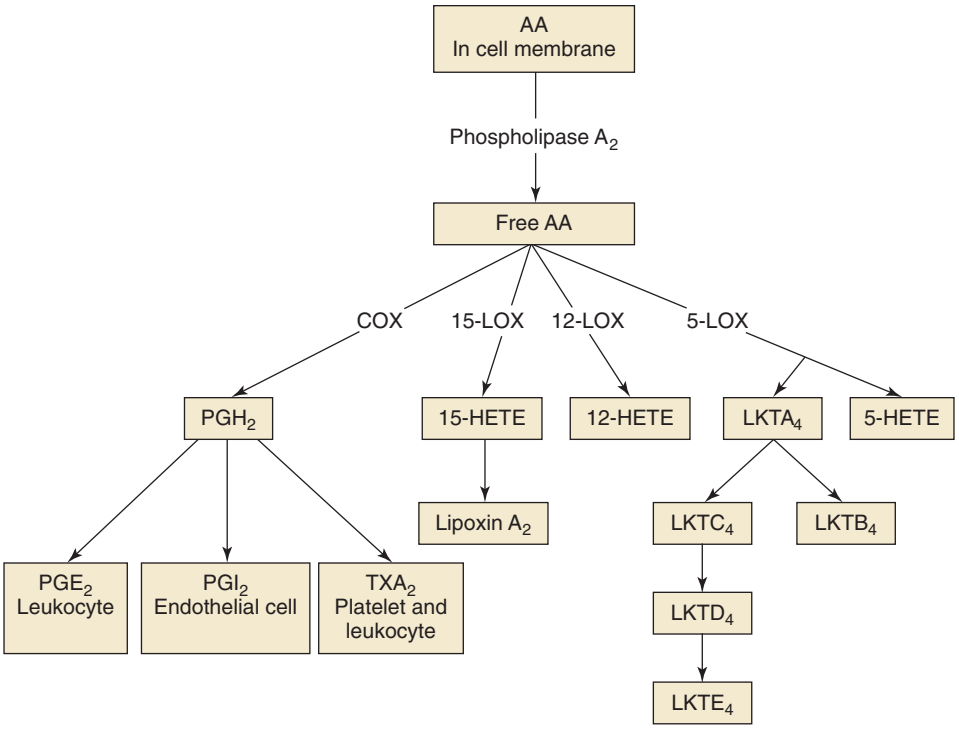

FIGURE 31-2 Metabolism of AA in various cells. Eicosapentaenoic acid (EPA) can substitute for AA as a substrate for COX and LOX systems. This may result in the release of compounds that are generally less active (TXA_3 and $LKTB_5$ instead of TXA_2 and $LKTB_4$) than those produced from AA. There is one exception with PGI_3, which is as active as PGI_2 as an antiplatelet and vasodilating substance. HETE, hydroxyeicosatetraenoic acid.

anti-inflammatory effects[148,149] indicating that the same compound, namely PGE_2, possesses both pro- and anti-inflammatory actions, whereas PGE_3 derived from EPA may apparently be less active than PGE_2.[130-132] This may explain some puzzling data showing benefits from PGE_2 in some inflammatory compartments, especially those where 4-series LKTs exert damaging effects.[150] In fact, one of the major inflammatory AA-derived eicosanoids of the 4-series LKTs is $LKTB_4$, which increases vascular permeability, is a potent chemotactic agent for leukocytes, and increases the generation of reactive oxygen species and production of inflammatory cytokines. $LKTB_4$ was recently shown to play an important role in the atherosclerotic process (using the intima-media thickness as a surrogate marker of atherosclerosis) in certain patients with a specific polymorphism (variant 5-LOX genotypes).[151] Interestingly, a protective effect of omega-3 PUFAs and a deleterious effect of omega-6 PUFAs were shown in that study, suggesting that contrary to the results of large randomized trials, where the protective effect of EPA plus DHA appeared to be confined to myocardial anti-arrhythmic effects,[7-9] long-chain omega-3 PUFAs may also be able to slow down the progression of the atherosclerotic process.[152] In addition, it is possible that incorporation of EPA and DHA in the plaque might have a stabilizing (anti-inflammatory) effect, as shown in a recent study,[152] allowing prevention of acute ischemic events. This suggests that EPA plus DHA may inhibit the generation of metalloproteinases,[153,154] compounds that are potentially involved in plaque vulnerability and ulceration and subsequent thrombotic complications. Further studies are obviously needed to support this assumption.

The PGE_2 and 4-series LKTs story illustrates the complexity of the health effects of eicosanoids and the necessity to be careful when using potent pharmacologic agents to manage them. As shown with the anti-COX-2 (coxib) agents, the ultimate outcome may be less appealing than previously expected, with a tragic increased risk of CHD complications.[121,122]

The EPA-derived 3-series of PGs and 5-series of LKTs are considerably less inflammatory than those derived from AA.[130-132] Increased consumption of omega-3 PUFAs results in increased proportions of omega-3 PUFAs, especially EPA in inflammatory cell phospholipids, at the expense of AA. This was shown to result in decreased production of PGE_2, TXB_2, and $LKTB_4$ by inflammatory cells and, at the same time, increased production of PGE_3, TXB_3, and $LKTB_5$. The functional significance of this is that the mediators derived from EPA are less potent than those derived from AA. It may be exaggerated, however, to say that EPA-derived eicosanoids are anti-inflammatory. Let it simply be said that they are less proinflammatory than the AA-derived eicosanoids.

Finally, recent studies have identified novel groups of mediators, termed E-series resolvins (for *resolution phase interaction products)* when derived from EPA by COX-2, and D-series resolvins (or docosatrienes and neuroprotectins) when derived from DHA by COX-2, which appear to have anti-inflammatory properties, especially during the resolution phase of the inflammatory process.[155] The relevance of this specific anti-inflammatory activity for vascular inflammation associated with atherosclerosis remains to be confirmed.[156]

Thus, the action of omega-3 PUFAs in antagonizing AA, the major inflammatory PUFA, appears to be a key anti-inflammatory effect of omega-3 PUFAs (Box 31-1). Another major question is whether omega-3 PUFAs have real anti-inflammatory effects that may occur downstream of altered eicosanoid production.

Omega-3 Polyunsaturated Fatty Acids and Inflammation

Proposed mechanisms by which omega-3 PUFAs may have anti-inflammatory effects are shown in Box 31-1. In addition

BOX 31-1 Anti-Inflammatory Effects of Omega-3 Polyunsaturated Fatty Acids

1. The 18-carbon omega-3 ALA (18:3n-3) decreases the synthesis of proinflammatory AA from the omega-6 LA (18:2n-6) through competition at the level of their common elongation and desaturation pathways (see Fig. 31-1).
2. The 20-carbon omega-3 PUFA EPA (20:5n-3) decreases the levels of AA in inflammatory cells. EPA replaces AA in membrane phospholipids (see Fig. 31-2).
3. EPA decreases the production of AA-derived inflammatory eicosanoids by decreasing the release of AA from cell membranes and competing at the levels of the COX and LOX enzyme systems.
4. EPA gives rise to a family of eicosanoid mediators that are analogues of those produced from AA (see Fig. 31-2) but are often less potent (less inflammatory).
5. Omega-3 PUFAs reduce the production of inflammatory cytokines (including TNF and interleukins) by leukocytes and other cells involved in the inflammation process through decreased production of TXA_2 and $LKTB_4$ (see text).
6. Omega-3 PUFAs induce production of the anti-inflammatory E-resolvins from EPA and D-resolvins from DHA (see text).
7. The omega-3 PUFAs EPA and DHA alter the expression of inflammatory genes via inhibition of the nonspecific transcription factor NF-κB (see text).

to competing with omega-6 PUFAs at various levels of PUFA metabolism, EPA and DHA were shown to inhibit the production of cytokines by leukocytes and other inflammatory cells in vitro and ex vivo.[157] In clinical studies, EPA plus DHA-rich fish oil supplementation was reported to result in decreased production of TNF and interleukins by leukocytes.[158] Also, diets enriched in ALA have been associated with reduced vascular inflammation and endothelial activation.[159] Which bioactive components (ALA itself or its metabolite EPA, or both) inhibit endothelial activation is not clear. In fact, De Caterina and colleagues showed that DHA and EPA significantly decrease cytokine-induced expression of adhesion molecules by endothelial cells.[160] This has the functional effect of decreasing the binding of leukocytes, a crucial step of vascular inflammation and atherosclerosis.[72,115] Interestingly, oleic acid (the precursor of the omega-9 PUFA ETA) was also shown to inhibit endothelial activation[161] and olive oil itself (the oil typically used around the Mediterranean Sea) had similar effects in middle-aged men.[162]

Some of the anti-inflammatory effects of omega-3 PUFAs may also be exerted at the level of gene expression. Although the extent of these effects in humans in vivo is not yet clear, animal studies indicate potentially significant effects on the expression of a range of inflammatory genes. For instance, omega-3 PUFAs were shown to decrease the cytokine-mediated induction of expression of COX-2, TNF-α, and various interleukins in cultured chondrocytes or human cartilage explants.[132] Similar data were reported with DHA and vascular endothelial cells.[160] This effect on gene expression was independent from the effect on eicosanoid production, and it is emerging that omega-3 PUFAs may exert this effect through direct actions on the intracellular signaling pathway that leads to activation of one or more transcription factors such as NF-κB (nuclear factor κB).[132] For instance, omega-3 PUFAs were shown to prevent NF-κB activation by TNF-α and to decrease endotoxin-induced activation of NF-κB by leukocytes.[161,163] Thus, in addition to directly decreasing the production of inflammatory eicosanoids and leukocyte cytokines, omega-3 PUFAs act by altering the expression of inflammatory genes.

Once mobilized from cell membrane phospholipids, 20-carbon PUFAs (either AA or EPA) are oxygenated into eicosanoids along various pathways including COX, LOX, P450 epoxygenase, and (nonenzymatic) isoprostane synthesis. In addition, free PUFAs are available to exert direct effects on membrane receptors and ion channels (e.g., to deploy anti-arrhythmic effects in the ischemic myocardium).[164]

As indicated above, the fate and distribution of AA or EPA metabolites depend on the cell type where they are formed. For example, leukocyte, endothelial and smooth muscle cells from arteries, as well as platelets, express PGE synthase and are, thus, all capable of producing proinflammatory PGE. Platelets express thromboxane A (TXA) synthase and elaborate the prothrombotic and vasoconstrictive TXA_2. Endothelial cells express prostacyclin synthase and synthesize the antithrombotic and vasodilating PGI_2. In addition to cell-specific synthesis, the biological effects of eicosanoids are governed by cell-specific receptor-dependent signaling pathways that define biological responses. Pharmacologic inhibition of eicosanoid synthesis has been the focus of intensive drug development, from aspirin to NSAIDs and specific coxibs. NSAIDs provide antipyretic, analgesic, and anti-inflammatory properties but the relative degree of these effects varies markedly from one compound to another. The NSAIDs also share the common side effects of gastrointestinal ulceration and renal function impairment.

With the recognition that aspirin inhibits platelet function via inhibition of thromboxane formation, the anti-thrombotic effects of these agents gained unique therapeutic emphasis. Because endothelial PGI_2 also has an antiplatelet action, non-selective inhibition of COX attenuates the antiplatelet effect of aspirin. Thus, in view of the irreversible inhibition of thromboxane formation in platelets by aspirin and of the differences in half-lives of platelet and endothelial COX, very low dose aspirin was found to provide optimal antithrombotic activity for prevention of thrombotic CVD complications.[135,136] Finally, the recognition that there are two different COXs led to the straightforward view that COX-2 is specifically responsible for the adverse proinflammatory effects of eicosanoids and that selective COX-2 inhibitors (with the coxibs) would provide adequate analgesia and anti-inflammatory effects (including within atherosclerotic plaque) without the gastrointestinal side effects due to gastric COX-1 inhibition and without platelet and endothelial cell effects.[136] Unfortunately, this clean mechanistic distinction between the COXs is an oversimplification.[121] In fact, inhibition of COX-2 appeared to be associated with suppression of prostacyclin synthesis (PGI_3 from EPA and PGI_2 from AA).[165] The complexity of the interactions between the different players in arterial physiology is illustrated by the fact that suppression of COX-2 results in an increasing flux of AA toward the different LOX pathways, with potential additional inflammatory effects. This may be especially important in the setting of inflammation in atherosclerotic plaque, as suggested by the study of Dwyer and coworkers on the role of LKTs in plaque progression.[151]

The deleterious cardiovascular effects COX-2 inhibition by coxibs reported in observational studies and in randomized trials may not be surprising.[121,122,166,167] It is important to note that these were observed in populations at low risk of CVD complications[166,167] and with nonselective NSAIDs,[168] suggesting that the increased risk of CVD complications seen with coxibs and other anti-inflammatory drugs is not a class of the drugs effects but a result of the inhibition of the inflammatory process itself.

Beyond the practical problems regarding the chronic treatment of painful inflammatory diseases such as arthritis, the COX-2 and coxib story raises several major questions regarding the theory of inflammatory atherosclerosis. The main one is that it is getting difficult to believe that vascular inflammation is a prominent feature in the development, as anti-inflammatory drugs, whatever their class, failed to prevent the risk of CVD complications in randomized trials (see Chapter 25). Time might have come to requestion our conception on the role of inflammation in atherosclerosis and its CVD complications. Thus for example, formation of fibrosis may actually be a key factor in lesion stabilization, why its modulation by an anti-inflammatory treatment may negatively impact on late healing, and maintain the increase the risk of plaque ulceration and recurrent ischemic events.

The potential role of omega-3 PUFAs in vascular inflammation and their important role in CVD may help us to open new roads in that difficult problem. From a biological point of view (see Box 31-1), omega-3 PUFAs appear to have anti-inflammatory properties that make them good candidates to reduce vascular inflammation and prevent atherosclerosis. However, large clinical trials did not suggest a strong effect of omega-3 PUFAs on atherosclerosis, but rather a direct effect on the risk of sudden cardiac death and ventricular arrhythmias, independently from any effect on the atherosclerotic process.[8,9] Thus, in line with the failure of NSAIDs and coxibs to reduce the risk of CVD complications, the anti-inflammatory omega-3 PUFAs had no significant effect on atherosclerosis in these trials. As the omega-3PUFAs in these trials were administered in general at the low doses of less than 1 g/day, one can requestion the presence of anti-inflammatory effects of such low dosages, and whether higher doses could be effective.

In fact, in a trial combining an increased intake of omega-9 and omega-3 fatty acids and a decreased intake of omega-6 PUFAs in the context of a Mediterranean diet,[7,19] a significant reduction of both fatal and nonfatal CVD complications was reported, suggesting major effects on the atherosclerotic process in addition to an effect on the risk of ventricular arrhythmias. The exact mechanisms of that protection remain to be elucidated. However, in recent randomized trials, the traditional Mediterranean diet was shown to be associated with significant anti-inflammatory effects, less endothelial dysfunction, and less vascular growth factor potentially implicated in atherosclerosis.[144,145] Whether these anti-inflammatory effects were adequately balanced to prevent vascular inflammation without altering the reparation-fibrosis process that stabilizes the atherosclerotic plaques is unknown but should be a working hypothesis. Taken together, these human data indicate that vascular inflammation is a complex multi-step process and atherosclerosis a multifactorial disease involving a great number of factors. When only considering dietary lipids, it is clear that essential PUFAs of both omega-6 and omega-3 families, saturated fatty acids, and omega-9 fatty acid are collectively involved. Thus, to be effective and safe, any anti-inflammatory approach of atherosclerosis and CVD should be prudent, probably non-pharmacologic, rather multifactorial and primarily dietary. This is in line with the well-accepted concept that CHD is a lifestyle disease that primarily needs lifestyle (especially dietary) changes to be prevented.

THE DIETARY APPROACH TO REDUCE CONVENTIONAL RISK FACTORS

Blood Cholesterol

Cholesterol level is associated with CHD mortality in certain but not all populations.[69,169] Cholesterol blood levels are partly regulated by diet. In the Seven Countries Study, marked differences in CHD mortality, dietary habits, and cholesterol distribution were observed in the different cohorts.[69,169] As the differences between other traditional risk factors were not as important as the dietary habits,[170] the cholesterol hypothesis was formlated to explain the difference in CHD mortality between populations. This set the basis for numerous trials initially with diets, then with increasingly potent lipid-lowering therapies, satins being at the forefront. Clearly, however, LDL cholesterol is not the only player. Thus, in the Seven Country study, CHD mortality at a cholesterol level of about 6 mmol/L was 3 times as high in Northern Europe as in Mediterranean Europe (18% vs. 6%), suggesting that factors other than cholesterol were important players in the disease. A new "diet heart hypothesis" was formulated that focus not only on cholesterol levels but also on other features of traditional diets of populations protected from CHD (e.g., vegetarian, Asian, or Mediterranean) that were not really tested, although they also impact cholesterol levels.[170] The Mediterranean diet has another handicap, it is mistakenly seen as a high-fat diet. The main features of Mediterranean diets, however, is small amounts of saturated and polyunsaturated fat and relatively high amounts of monounsaturated fat.[171-173] Other features are large amounts of fibers that influence lipid metabolism. A consensus now exist that diets low in saturated and polyunsaturated fat but rich in oleic acid results in a significant reduction of total and LDL cholesterol with little effect on triglycerides and small and neutral or a HDL cholesterol.[171-173] Such a diet is recommended in secondary prevention, especially after a myocardial infarction where it was shown effective in preventing adverse ischemic events.[4,7,19] The lipid-lowering effect of the diet is similar to the prudent Western diet suggesting that the cardioprotective benefits could be partly independent of the cholesterol reducing effects.

Blood Pressure

High blood pressure (HBP) is a common problem in many Western countries and represents a major cardiovascular risk factor. The relation between blood pressure and CHD is continuous with no abrupt increase in risk at levels of blood pressure diagnostic of HBP.[174] The preventive efforts should therefore be dictated not only by a given number but also by the risk in a given patient. Another important feature is that even small reductions in blood pressure impact on prognosis. For instance, a 5 mm Hg reduction in diastolic blood pressure reduces the risk of stroke by 35% to 40%.[176] Most post-MI patients are prescribed a hypotensive drug as standard therapy, although many discontinue the drug because of side effects.[175] Clearly, however, a nondrug therapy with lifestyle modifications could be a valid alternative, especially in the long term.

Data from the Seven Countries Study provided important information on the role of diet to prevent high blood pressure-related CHD complications.[177] The study showed many variations in CHD mortality across various populations at each level of systolic or diastolic blood pressure. At a diastolic blood pressure level of 90 mm Hg, CHD mortality was 3 times lower among Mediterranean people than those in the United States and Northern Europe, again suggestive of a protective effect of the Mediterranean diet. The same reasoning probably applies to the Asian (Japanese) diet. Another question is whether dietary factors influence blood pressure. High sodium intake and the excess of binge alcohol drinking certainly increase blood pressure.[178]

Recent investigation looked at the effects of the Mediterranean diet pattern on blood pressure.[179-181] As could have

been predicted, the dietary pattern was associated with the production and release of several major vasodilators, including nitric oxide,[182] resulting in lower blood pressure and lower rates of hypertension.[179-182]

An adequate intake of certain minerals (sodium, potassium, magnesium, and calcium), rather than the sole restriction of sodium, was also proposed as an explanation.[183] The intake of n-3 fatty acid which also lower blood pressure in subjects with hypertension[184] proportionally to the changes in phospholipid n-3 fatty acids, however n-6 fatty acids had no such effects, which suggests that it is specific to the n-3 family. This data implies a benefit of n-3 fatty acids in modulating (endothelial) factors regulating blood pressure.

The Dietary Approaches to Stop Hypertension (DASH) study compared the effect on blood pressure of a diet rich in fruits and vegetable, to a "combination" diet rich in fruits, vegetables, low-fat dairy products, and low in saturated and total fat.[185] Although not typical, the "combination" diet was the one closest to Mediterranean diet. In the first DASH trial, which did not modify sodium intake, the "combination" diet decreased systolic blood pressure by 5 to 6 mm Hg in subjects with normal blood pressure and by twice as much in patients with mild hypertension. These reductions match those observed with antihypertensive medications, at no cost and no side effects. The DASH trial confirmed a previous meta-analyses of observational studies that suggested that dietary factors other than sodium could markedly affect blood pressure.[183] The second DASH trial added in the protocol of different levels of dietary sodium.[186] Again blood pressure was substantially decreased and the decrease was greater at any level of sodium intake, with the "combination" DASH diet than with the control diet.[186] Combining a reduction of sodium intake to levels below 100 mmol/day to the DASH diet lowers blood pressure to a greater extent than either of the two separately, showing a potentiating effect. Whether these dietary changes may reduce the risk of CHD remains to be demonstrated.

Endothelial Dysfunction

Endothelial dysfunction is one mechanism that may contribute to the association between high blood pressure and CHD. The endothelium, the innermost layer of all blood vessels, is critical in determining the contractile state of the underlying smooth muscle.[187] Through the release of a number of substances, the endothelium modulates several other functions, including platelet aggregation, leukocyte adhesion and migration, smooth muscle cell proliferation and lipid oxidation, all of which contribute to the atherosclerotic process. The term *endothelial dysfunction* has been used to describe a constellation of abnormalities in these regulatory actions of the endothelium, and endothelial dysfunction has been reported in conditions such as HBP, diabetes, and hyperhomocysteinemia. For instance, in patients with HBP, there is an imbalance in the bioactivity of endothelial factors with proatherosclerotic (endothelin-1) and antiatherosclerotic (nitric oxide) actions[188] that may explain why HBP is a risk factor for CHD, regardless of whether endothelial dysfunction is a cause or a consequence of HBP. Coronary endothelial dysfunction by itself was indeed shown to be of prognostic significance in patients with CHD.[189] Endothelium-derived nitric oxide (NO) plays an important role in the regulation of tissue perfusion, and evidence is accumulating that NO-dependent vasodilatation and NO availability are impaired in the coronary arteries of patients with CHD or with CHD risk factors such as high blood cholesterol or high homocysteine levels. Interestingly, folic acid therapy, either as chronic oral supplementation or as acute intra-arterial administration of the active form of folic acid (5-methyltetrahydrofolate), restores the impaired endothelial function even in patients with CHD risk factors but normal serum folic acid and homocysteine levels.[190,191] The administration of folic acid is, however, of no clinical benefit.[191a,191b] A deficieny in NO-synthase cofactor, tetrahydrobiopterin (BH4), may also blunt the endothelium-dependent vasodilatation in humans.[192] The deficiency uncouples the L-arginine-NO pathway, resulting in increased formation of oxygen radicals. Intra-arterial or intracoronary infusion of BH4 can improve the endothelial dysfunction in patients with various clinical manifestations.[192,193] As an interaction could exist the active form of folic acid is involved in the endogenous regeneration of BH4, between the arginine-NO-synthase pathway and folic acid.

Another cause of endothelial dysfunction in the context of traditional risk factors of CHD (including HBP and insulin resistance) is elevated levels of asymmetric dimethyl arginine (ADMA), that also inhibits the production of NO.[194] Whereas blood ADMA levels appear influenced by dietary fats, further studies are required to clarify the relationships between the dietary factors (folates, antioxidants) involved in the regulation of NO-synthase and ADMA metabolism.

A diet rich in vegetables and fruits and the traditional Mediterranean diet provide large amounts of folates. Consumption of legumes (dry beans and peas, peas, peanuts, peanut butter, lentils), which is another typical Mediterranean habit has been shown to be associated with a reduced risk of CHD.[195] Tree nuts, such as walnut, and hazelnut are also a usual ingredient of vegetarian and Mediterranean diets. Most nuts are also rich in arginine, an amino acid serving as substrate for the synthesis of NO. Because of the importance of NO in cardiovascular diseases, there has been growing interest over the past 10 years in using arginine to prevent and treat cardiovascular diseases.[196] Compelling evidence shows that enteral or parenteral administration of arginine reverses endothelial dysfunction associated with major CHD risk factors in a way very similar to that observed with folic acid and BH4. Endothelial arginine is derived from the plasma, via intracellular synthesis with citrulline as a precursor, and from the net degradation of intracellular proteins. However, food is the ultimate source of arginine for the body. Dietary arginine intake (the main source being animal products for the Western population) by an adult has been estimated to be around 5 g/day.[196] Because of arginase activity in the intestine and of the limited digestibility of protein-bound arginine, it is assumed that only 50% of dietary arginine enters systemic circulation. The adequate daily arginine requirement is difficult to assess and probably varies in relation with the presence or absence of CHD risk factors, which are often associated with the presence of endogenous NO-synthase inhibitors. It probably also varies with the amount of folates in the diet, since the active form of folic acid is indispensable for the regeneration of BH4. The amount of arginine found in the typical Western diet appears at best barely sufficient to cover the daily requirements of a healthy individual. Furthermore, in the presence of CHD risk factors or established CHD, the intake of arginines tendeat to decrease as patients less animal foods because they are considered "non-friendly for the heart" although protein-rich. The exact requirements of these patients remain to be determined but previous studies suggested 6 to 9 g above dietary supplies could be required to reverse endothelial dysfunction. Other factors, such as impaired intestinal absorption, competition with other amino acids (in particular lysine) for cell transport, and the amount of folates in the diet, were not taken into account in these calculations. Whatever the clinical condition, nuts are a convenient natural source of arginine, not only because of the high concentration of arginine in most nuts but also because of the high content of

folates and vitamin B_6, the major cofactors involved in the catabolism or recycling of homocysteine. Although controlled trials testing the effects of L-arginine supplementation were obviously undersized, the results have been so far quite disappointing.[197]

Type 2 Diabetes

Patients with type 1 diabetes do not raise specific dietary issues beyond the usual diabetic diet to control blood glucose once the insulin treatment is correctly administered. In contrast, the number of patients with type 2 diabetes or insulin resistance is increasing rapidly and is of daily concern for cardiologists.

Type 2 diabetes mellitus is associated with a three- to fourfold increase in the incidence of CHD.[198] A large part of the decline in CHD mortality in most Western populations has been but this decline attributed to reduction of risk factors, was less marked among diabetics, particularly women. Apart from calorie restriction, the composition of the diet of patients with type 2 diabetes remains controversial. The emphasis currently is on a diet low in saturated fatty acids. A reduction of the total fat intake is also suggested when weight loss is a primary issue. As most type 2 diabetics require weight loss a low-fat diet is commonly prescribed. A diet high in monounsaturated fats improves metabolic control better than a low-fat, high-carbohydrate diet, and should be preferred.[200] On the basis of a meta-analysis, it is clear that diets high in monounsaturated fat improve lipoprotein and blood glucose profiles and also lower blood pressure.[200] This type of diet may also reduce the susceptibility of LDL particles to oxidation and thereby reduce their atherogenic potential; in addition, it does not induce weight gain, provided that energy intake is controlled. Thus, in theory, diets low in saturated fatty acids but rich in monounsaturated fats (two of the main characteristics of the Mediterranean diet) are advantageous for the prevention of CHD in diabetics. Actually, several studies have successfully investigated that adoption of a Mediterranean-type diet favorably influences insulin resistance, metabolic syndrome, diabetes and their cardiovascular complications.[201-204]

An important message from the UK Prospective Diabetes Study (UKPDS) and recent trials is that in the prevention of CHD in type 2 diabetics, is that it is unwise to focus on single risk factors,[205] but that all known risk factors should be tackled simultaneously, including high blood glucose and hypertension. Also, because of a high risk of SCD in diabetics, specific recommendations aimed at preventing SCD should be given as in non-diabetic patients (see earlier discussion). Classical risk factors fail to explain the excess CHD rate in Indians as compared with Europeans, although the high prevalence of diabetes in India may play a part.[206] When exploring the contribution of dietary fatty acids in Indian diabetics, large differences in phospholipids fatty acids were noted, most notably lower concentrations of n-3 fatty acids,[207] which could contribute to their high CHD mortality rates.

Considering all of these observations, it seems that the optimal diabetic diet may be a low-calorie Mediterranean diet. Not only does this diet protect the heart and reduce blood pressure, but certain components of the Mediterranean diet (n-3 fatty acids in association with vegetables and legumes) can improve glucose tolerance and delay the occurence of overt diabetes.[208] These human data confirm animal research that showed the importance of n-3 fatty acids in the action of insulin in various experimental models.[209] Thus, although further studies are required, in particular about the physical structure of foods to modulate glucose metabolism and insulin resistance,[210] it seems that diabetic patients should be instructed on the basic principles of the Mediterranean diet.

A MINIMUM CLINICAL PRIORITY DIETARY PROGRAM

Despite the increasing evidences that dietary prevention is critical in the post-AMI patient, many physicians and their patients remain rather poorly informed about the potential benefit of alimentation to reduce cardiac mortality, the risk of new CHD complications, and the need for recurrent hospitalization due to the lack of knowledge transmission.[211] For this reason we propose a minimum dietary program that every CHD patient, whatever his or her medical, familial, and social environment, should know and follow. The minimum Mediterranean dietary program should include:

1. A reduction in consumption of animal saturated fat (for instance, by totally excluding butter and cream from the daily diet and drastic reduction of fatty meat) and increase consumption of n-3 fatty acids through increased intakes of fatty fish (about 200 g, twice a week). For patients who cannot eat fish (for any reason), the use of 2 capsules a day of n-3 fatty acids (for instance, a mix of alpha-linolenic acid and long-chain n-3 fatty acids) is the best alternative. The way of cooking fish is important. It implies to avoid salted, deeply fried fish in saturated or polyunsaturated fat. It should also be known that n-3 fatty acid supplementation will add to the protection if associated with adequate dietary modifications discussed all along in the chapter.
2. A high intake of anti-inflammatory fatty acids (oleic acid and n-3 fatty acids) and a decrease intake of pro-inflammatory fatty acids (n-6 fatty acids). The best way is to exclusively use olive oil and canola oil for cooking and salad dressing and canola oil-based margarine instead of butter and polyunsaturated oils and margarines.[212,213] Patients should also systematically reject convenience food prepared with fats rich in saturated, polyunsaturated, and trans fatty acids.
3. An increase intake of natural antioxidants (vitamins and trace elements) through increased consumption of fresh fruits and vegetables and tree nuts.[214]
4. Moderate use of alcoholic beverages (1 or 2 drinks/day), preferably wine and preferably during the evening meal, but not before driving or making a hazardous technical manipulation.
5. A reducetion in sodium intake (below 100 mmol/day if possible) knowing that it is a very difficult task at the present time because of the high sodium content of many natural (including typical Mediterranean foods such as olives and cheeses) and convenience food.

To conclude, patients (and physicians) should keep in mind that an optimal (and individual) dietary prevention program should be managed under the guidance of a professional dietician aware of the most recent scientific advances in the field.

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CHAPTER 32

Exercise Training After an Acute Coronary Syndrome

Anil Nigam and Martin Juneau

CLINICAL BENEFITS

Numerous publications have documented the efficacy of exercise-based cardiac rehabilitation (CR) after myocardial infarction (MI) or coronary artery bypass surgery. Because most studies published were underpowered to detect significant mortality reductions, many meta-analyses were performed to address this issue. Three recent meta-analyses[1-3] have confirmed earlier reviews published in the late eighties.[4,5]

In their publication, Clark and colleagues[1] reviewed 63 randomized trials including a total of 21,295 patients. For the 40 trials that reported all-cause mortality, representing 16,142 patients, the overall mortality reduction was 47% at 2 years. The risk of recurrent MI was reduced by 17% over a mean follow-up of 12 months. Seven trials reported a follow-up of at least 5 years and documented a sustained long-term benefit with a reduction of all-cause mortality of 23%. The treatment effect did not differ between the different types of interventions, that is, exercise only or exercise associated with a comprehensive risk factor reduction program.

Taylor and coworkers[2] reviewed 48 trials with a total of 8940 patients in their systematic review. Their results show that exercise-based CR is associated with a 20% reduction in all-cause mortality and a 26% reduction in cardiac mortality (Fig. 32-1). There was no significant reduction in the incidence of recurrent nonfatal MI.

A systematic review by the Cochrane collaboration published initially in 2001 and revised in 2005[3] studied 51 trials for a total of 8440 patients. They reported a 27% reduction in all-cause mortality and a 31% reduction in cardiac mortality. Combined events (nonfatal MI, coronary artery bypass surgery, and angioplasty) were reduced by 19%. There was no evidence of risk reduction for recurrent nonfatal myocardial infarction.

COST-EFFECTIVENESS OF EXERCISE-BASED CARDIAC REHABILITATION

A review of 15 studies on the economic impact of exercise-based CR was published by Papadakis and colleagues in 2005.[6] The authors concluded that the range of cost per life-year gained was between $2193 and $28,193 and from $668 to $16,118 per quality-adjusted life-year gained.

Ades and colleagues[7] studied the cost effectiveness of CR after myocardial infarction. Their results show a cost of $2130 per life-year saved in the late 1980s and $4950 per life-year saved in 1995. They concluded that exercise-based CR is more cost effective than thrombolytic therapy, coronary artery bypass surgery and cholesterol-lowering medication, although less cost effective than smoking cessation programs.

Fidan and coworkers[8] performed an economic analysis of treatments to reduce coronary heart disease mortality in England and Wales, and concluded that exercise-based CR was among the most cost-effective interventions. The cost per life-year gained was 1957 pounds sterling compared to angiotensin converting enzyme inhibitors at 3398 pounds, and to statins at 4246 pounds per life-year gained.

A Canadian government[9]–sponsored study concluded that exercise-based CR was cost-effective with an estimated cost of 4950 canadian dollars per life-year gained.

Underutilization of Exercise-Based Cardiac Rehabilitation

Despite the proven benefits of exercise-based CR, it is still greatly underutilized in North America and Europe. Recently Suaya and coworkers[10] studied the use of CR in 267,427 Medicare beneficiaries and found that CR was used in 13% of post-myocardial infarction patients and 31% of post-coronary artery surgery patients. The adjusted CR use rate varied greatly

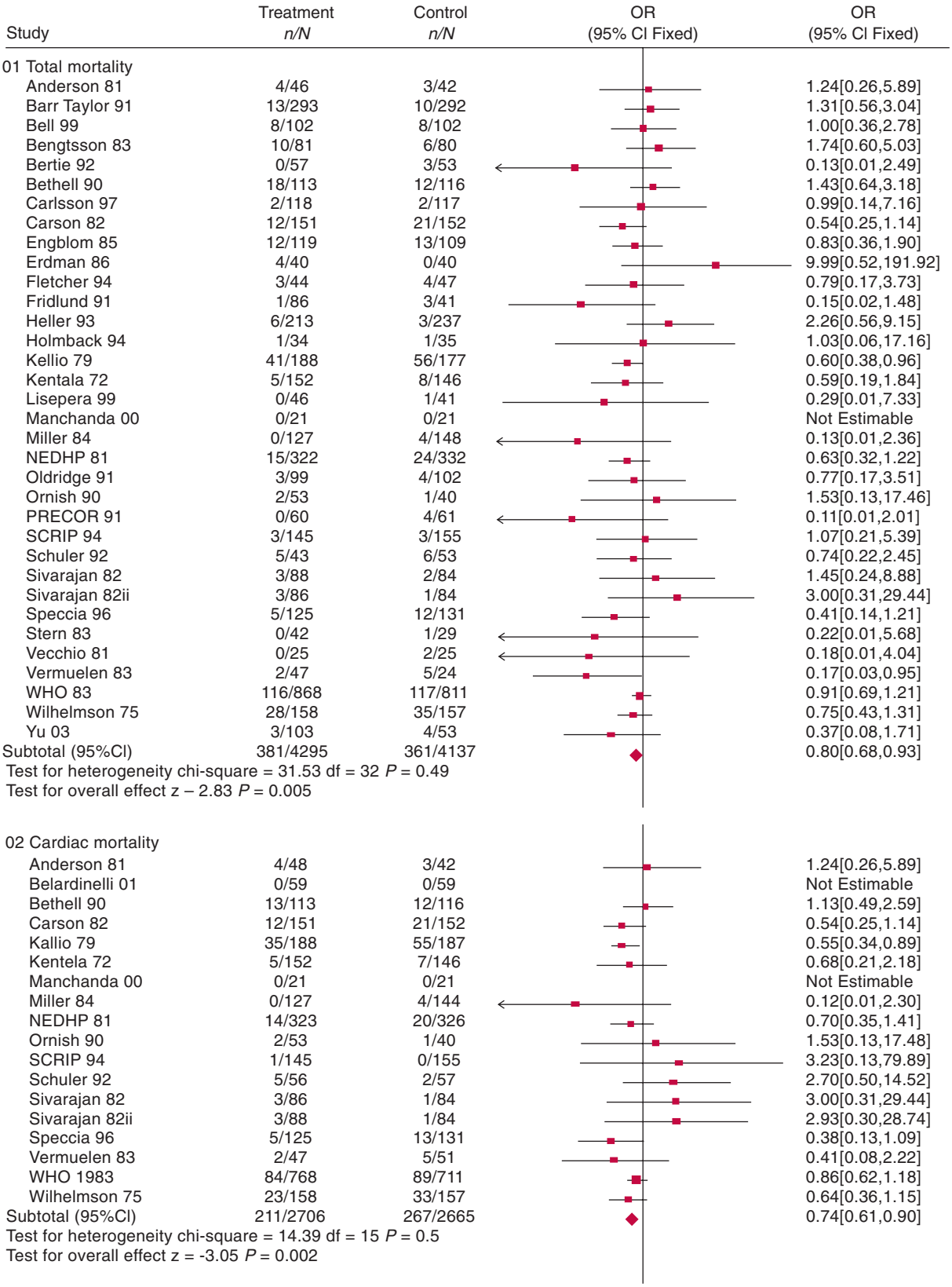

FIGURE 32–1 Summary of the effects of exercise training on total and cardiac mortality in patients with coronary heart disease. *(With permission from Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682-692.)*

(ninefold) among states from 6.6% in Idaho to 53.5% in Nebraska. Underuse in this study and others[11] was associated with older age, female gender, nonwhite ethnic origin, significant comorbidities, and long distance from the CR program.

CARDIOPROTECTIVE MECHANISMS OF EXERCISE

The cardioprotective effects of exercise in patients following acute coronary syndromes (ACS) as well as in those with stable coronary heart disease (CHD) are multifactorial and appear to be related to improvements in endothelial function, inflammation, autonomic regulation of cardiovascular function, and risk factor control, as well as potential antithrombotic effects and effects related to ischemic preconditioning (Box 32-1).

The Endothelium

Both acute and chronic exercise have been shown to improve endothelial function by increasing shear stress-induced flow-mediated arterial vasodilatation.[12,13] Increased shear stress on the arterial wall during exercise leads to increased production and release of nitric oxide (NO) from endothelial cells.[14] A single bout of vigorous exercise was recently shown to improve endothelial function in the rat, with regular exercise for 6 weeks further improving endothelial function.[12] Hambrecht and colleagues in a randomized, controlled trial involving 19 patients with stable CHD, demonstrated that an intensive in-hospital aerobic exercise training program of 4 weeks duration was able to improve coronary endothelial function and coronary blood flow.[15] A follow-up study assessing the effect of a 5-month home-based exercise training program in the same participants showed that home-based training (albeit at lower intensity and frequency) was sufficient to partially sustain the improvements in endothelial function achieved after the initial 4-week in-hospital program, suggesting the effects of exercise on endothelial function are dose-dependent.[16] In a randomized, controlled trial of 12 weeks' duration in 18 patients with stable CHD, Edwards and coworkers showed that CR with aerobic exercise training was able to improve peripheral endothelial function as measured via brachial ultrasonography.[17] Similarly, in a case-control study of 58 patients with stable CHD, a 10-week supervised exercise training program involving predominantly lower-limb activities (treadmill, stationary bicycling), resulted in an improvement in lower limb endothelial function while endothelial function remained unchanged in the non-training control group.[18] Walsh and coworkers also showed in a randomized, controlled, crossover study in 10 patients with stable CHD that an 8-week combined aerobic and resistance training program was able to improve conduit vessel endothelial function, indicating the effects of exercise on the endothelium are not limited to a single vascular bed but are systemic.[19] Two studies have specifically assessed the effect of exercise training on endothelial function following acute coronary syndromes. Firstly, Hosokawa and colleagues in 41 patients with recent myocardial infarction, showed that subjects performing regular exercise had improved coronary endothelial function after 6 months relative to non-exercisers.[20] Finally, Vona and colleagues in a randomized, controlled trial in 52 patients with a recent uncomplicated first myocardial infarction, demonstrated that a 3-month moderate-intensity aerobic exercise program improved brachial artery endothelial function, while detraining resulted in a deterioration in vascular function.[21]

Several mechanisms have been put forth to explain the beneficial effects of chronic exercise on endothelial function, namely by re-establishing the balance between NO production and degradation. Firstly, Hambrecht and coworkers showed in patients with multivessel CHD undergoing coronary bypass surgery, that a 4-week in-hospital aerobic exercise training program led to increased shear stress-induced Akt-dependent phosphorylation of endothelial nitric oxide synthase (eNOS) and eNOS expression in left internal mammary endothelial cells relative to inactive controls.[22] Exercise training also appears to reduce NO degradation by reducing oxidative stress through decreased expression of angiotensin-II (ATII) subtype I receptor, reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase-derived production of reactive oxygen species (ROS) and prevention of ATII-induced vasoconstriction of conduit arteries.[23] Finally, aerobic exercise might improve endothelial function by stimulation of endothelial progenitor cell (EPC) formation and release from bone marrow, resulting in repair of damaged vascular endothelium. Adams and colleagues showed in CHD patients with exercise-induced ischemia that a single bout of exercise was sufficient to increase blood EPC levels, whereas EPC levels remained unchanged in CHD patients without ischemia and in healthy volunteers.[24] In work by the same group, a 4-week exercise training program in patients with symptomatic peripheral vascular disease was shown to significantly increase blood EPC levels, whereas EPC levels remained unchanged in revascularized patients as well as in CHD subjects who trained below the ischemic threshold.[25] These data suggest that ischemia plays an important role in promoting EPC formation and release, perhaps through increased levels of vascular endothelial growth factor. Finally, in 20 patients with CHD and/or cardiovascular (CV) risk factors, a 12-week running program was shown to significantly increase circulating EPC levels, which correlated with improved endothelial function.[26] No studies have evaluated the effect of exercise training on EPC levels in patients following an acute coronary syndrome.

BOX 32-1 Cardioprotective Mechanisms of Exercise

1. Improved endothelial function and passivation of atherosclerotic plaques
2. Reduction in systemic inflammation
3. Beneficial effects on the autonomic regulation of cardiovascular function
4. Improvement in risk factor control
   - Increase in HDL-cholesterol concentrations
   - Reduction in triglyceride concentrations
   - Reduction in blood pressure
   - Reduction in body weight
   - Reduction in insulin resistance and improvement in glucose metabolism
5. Potential anti-thrombotic and anti-platelet effects
6. Intrinsic mechanisms
   - Ischemic preconditioning with reduced myocardial damage during prolonged ischemia
   - Prevention of reperfusion-induced ventricular arrhythmias

Atherosclerosis Progression/Regression

Three studies have evaluated the effect of exercise training in combination with lifestyle interventions on angiographic coronary artery disease. The first was the study by Schuler and colleagues in which 113 patients with stable angina were randomly assigned to either a usual care group or to an intervention group consisting of daily exercise training (approximately 4 hours per week) in combination with a low-fat diet.[27] After 12 months of treatment, atherosclerosis progression was significantly reduced in the intervention group relative to the

control group. In the Stanford Coronary Risk Intervention Project, 259 men and 41 women with angiographically documented coronary atherosclerosis were randomly assigned to either a usual care control group or to a multifactor risk reduction program which included a low-fat diet, exercise training, smoking cessation, weight loss, and lipid-lowering medication.[20] After 4 years, the progression of atherosclerosis was reduced by 47% ($P < .02$), and hospitalization for cardiac events was reduced by 39% ($P = .05$) in the multifactor risk reduction group. Finally, in the Lifestyle Heart Trial, 48 patients with moderate to severe coronary heart disease were randomly allocated to either a usual care group or to an intensive lifestyle intervention group (low-fat vegetarian diet, regular aerobic exercise, smoking cessation, stress management, and group psychosocial therapy) and followed for 5 years.[21] At the end of follow-up, average percent diameter stenosis was reduced by 8% in the intervention group, while this parameter increased by 28% in the usual care group ($P = .001$ between groups). Importantly, the risk of a cardiac event was 2.5-fold higher in the control group relative to the intervention group. These studies highlight the dramatic reduction in cardiac events with a multifactor risk reduction program including regular aerobic exercise, despite only modest changes in angiographic atherosclerosis burden. More recently, Hambrecht and colleagues randomized 101 men with class I to III angina pectoris and evidence of one coronary artery with greater than or equal to 75% diameter stenosis to either aerobic exercise training for 1 year or percutaneous coronary intervention (PCI).[28] Subjects in the exercise training group had a higher event-free survival relative to those in the PCI group (88% vs. 70%, $P = .023$) and better functional capacity at the end of 1 year. As with early statin studies that showed a significant reduction in clinical events despite modest changes in plaque burden, the striking clinical benefits with exercise training are now attributed to improved endothelial function and passivation of atherosclerotic plaques.[29-32] No studies have evaluated the impact of regular exercise on progression or regression of atherosclerosis following ACS.

Inflammation

Inflammation plays a major role in the pathogenesis of atherosclerosis and CHD.[33] A very sensitive marker of inflammation and one of the most studied biomarkers in patients with CHD is the acute-phase reactant C-reactive protein (CRP).[34] Elevated CRP levels are associated with a significantly higher risk of morbidity and mortality in otherwise healthy men and women.[35,36] A recent meta-analysis of studies evaluating the relationship between exercise and CRP in healthy men and women showed that regular exercise produces an anti-inflammatory effect associated with lower CRP levels.[37] A 12-week aerobic exercise training program was shown to significantly reduce levels of several inflammatory markers including CRP in patients with stable CHD.[35] Similarly, a 12-week aerobic training program conducted in 32 patients with CHD and/or CV risk factors demonstrated a reduction in chemokines, interleukin-8, and monocyte chemoattractant protein-1 as well as a reduction in matrix metalloproteinase-9.[38] In 39 patients randomized to either a control group or exercise training consisting of 1 month high-frequency aerobic training (90 minutes per day) followed by home-based moderate-frequency training (30 minutes per day), high-frequency training was associated with a significant reduction in several proinflammatory cell adhesion molecules, with a blunted response at 5 months after moderate-frequency training.[39] These data suggest a dose-response effect of chronic exercise on inflammation. Finally, in 101 male patients with symptomatic CHD randomized to exercise training or PCI and followed for 2 years, exercise training was associated with a significant reduction in both CRP and interleukin-6 levels while no changes were observed in inflammatory parameters in the PCI group.[24] No studies have specifically assessed the impact of exercise training on inflammatory markers in patients after ACS.

The Autonomic Nervous System

Measures of autonomic regulation of CV function and cardiac vagal activity including heart rate variability (HRV) and baroreflex sensitivity (BRS), have been shown to be powerful, independent prognostic indicators in post-MI patients.[40] Both decreased HRV and BRS, indicative of a sympathovagal imbalance, are associated with an increased risk of ventricular arrhythmias and sudden cardiac death following myocardial infarction.[41] To date, nine studies have been performed in post-MI patients to study the effects of chronic exercise training (3-6 month programs) on cardiac autonomic control, of which the majority showed a decrease in resting heart rate and improved sympathovagal balance.[42-51] While the mechanism of exercise-induced augmentation of cardiac vagal tone remains to be elucidated, data suggest that both peripherally and centrally produced NO (in neuronal cells) may exert a facilitation effect on baroreflex afferent-mediated activity in the nucleus tractus solitarius and increase central and peripheral vagal nerve activity.[42]

Risk Factor Control

Lipid Control

A recent review of the impact of exercise on blood lipid levels in the noncoronary population indicates a predominant effect of exercise training on high-density lipoprotein (HDL)-cholesterol and triglycerides with few and variable effects on total and low-density lipoprotein (LDL)-cholesterol.[52] Cross-sectional and prospective studies indicate that a training volume of 15 to 20 miles (24-32 km) per week of brisk walking or jogging corresponding to 1200-2200 kcal/week energy expenditure can increase HDL-cholesterol levels by 2 to 8 mg/dL, while reducing triglyceride levels by 8 to 20 mg/dL. A threshold value of 900 kcal appears to be required to raise HDL-cholesterol with a subsequent dose-response effect.[52,53] In a meta-analysis of randomized trials in patients with CV disease, aerobic exercise training was associated with a 9% (3.7 ± 1.3 mg/dL) increase in HDL-cholesterol, and an 11% (19.3 ± 5.4 mg/dL) reduction in triglycerides with no significant change in total or LDL-cholesterol.[54]

Blood Pressure

In a meta-analysis of 54 randomized trials conducted in individuals with and without hypertension, aerobic exercise training for 2 weeks or more was shown to lower systolic blood pressure by 3 to 4 mm Hg and diastolic blood pressure by 2 to 3 mm Hg, with a greater blood pressure-lowering effect noted in hypertensive patients.[55] Although less well studied, resistance training has been shown to lower diastolic blood pressure by 3 to 4 mm Hg.[56] Similarly, a regular walking program of ≥4 weeks or more duration was shown to significantly lower diastolic blood pressure by 2 to 3 mm Hg with no significant effects on systolic blood pressure according to a recent systematic review.[57] Finally, in a review of studies on exercise-based CR programs in patients with CHD including prior MI, exercise training (median program duration of 3 months) was associated with a significant 3.2 mm Hg reduction in systolic blood pressure ($P = .005$) with no significant reduction in diastolic blood pressure.[2]

Weight Loss

Several systematic reviews have evaluated the impact of aerobic exercise training on weight loss in overweight and

obese subjects.[58-60] All showed significant weight loss ranging from 2 to 11 kg with programs lasting 12 weeks to 1 year. Exercise training was also more effective for weight reduction if combined with a dietary intervention. Two studies of the effects of exercise-based CR of 3 months' duration on weight loss found either no weight loss or modest weight loss (2%) solely in obese subjects.[61,62] A long-term (≥6 months' duration) exercise training program was recently shown to result in modest but significant weight loss in CHD subjects with metabolic syndrome.[63]

Insulin Resistance Syndromes

A large body of literature has demonstrated the beneficial effects of exercise on insulin resistance syndromes including metabolic syndrome and type 2 diabetes mellitus. The subject is beyond the scope of this book and the reader is invited to consult one of the many excellent review articles on the subject. In a randomized trial of 29 patients with CHD, a 12-week supervised exercise training program in the absence of weight loss was not associated with an improvement in insulin sensitivity.[64] As noted earlier, a long-term exercise training program in CHD patients with the metabolic syndrome was shown to reduce obesity-related parameters including body weight, body mass index, and insulin resistance (Fig. 32-2).[63]

Antithrombotic Effects of Exercise

The effects of exercise training on hemostasis and coagulation remain unclear. Paradoxically, acute vigorous exercise has been shown to cause activation of blood coagulation, acceleration of blood fibrinolysis, and effects on platelet function, whereas moderate-intensity exercise results solely in activation of fibrinolysis.[65,66] Whether these findings possess clinical relevance, however, remain unclear. Information regarding the effects of chronic exercise training are incomplete and contradictory, most probably due to differences in study populations, training duration and intensity, and the analytical methods used.[65,66] Similarly, acute exercise has been shown to potentially increase platelet activation, whereas the effects of chronic exercise training on platelet function remain unclear.[65] Future studies are required to evaluate the effects of both aerobic and resistance training on hemostasis and platelet function in patients with CHD.

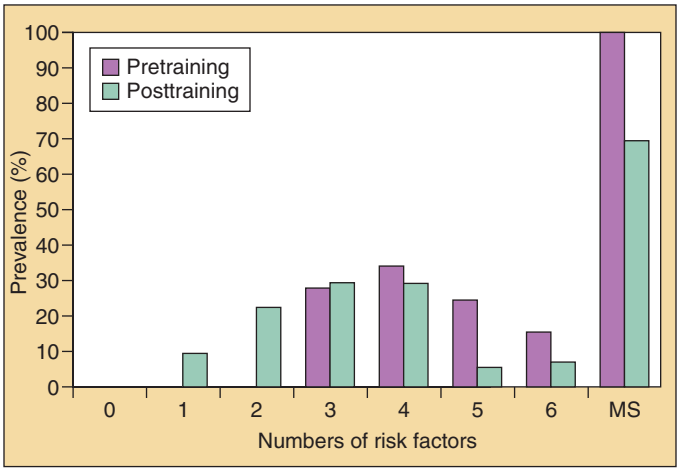

FIGURE 32–2 Frequency distribution of metabolic syndrome risk factors (ATP III criteria) among CHD patients before and after a long-term (6-month) cardiac rehabilitation program. $P < .0001$. MS, metabolic syndrome. *(Adapted with permission from Gayda M, Brun C, Juneau M, et al. Long-term cardiac rehabilitation and exercise training programs improve metabolic parameters in metabolic syndrome patients with and without coronary heart disease. Nutr Metab Cardiovasc Dis 2008;18:142-151.)*

Cardioprotective Effects of Exercise: Intrinsic Mechanisms

Ischemic preconditioning refers to the phenomenon whereby exposure to brief episodes of ischemia prior to a prolonged ischemic period followed by reperfusion leads to delayed myocardial injury and smaller infarct size.[67,68] This phenomenon was first described in the rat model in 1978 and has since been confirmed in a series of animal studies, although the exact underlying mechanisms remain unclear.[69,70] Several lines of evidence suggest the same phenomenon occurs in humans. For example, preinfarction angina is associated with smaller infarct size, a lower incidence of congestive heart failure, and decreased mortality.[71,72] During PCI, successive balloon inflations have been shown to result in decremental ST-segment elevation.[73] Finally, the phenomenon of warm-up angina whereby patients may present angina upon initiation of exercise, which then fails to return upon resumption of exercise, is also thought to be a manifestation of ischemic preconditioning,[74] which theoretically could provide protection during longer periods of ischemia such as during myocardial infarction.

Summary

The mortality benefits of exercise-based CR following ACS appear to be related to multiple cardioprotective mechanisms, including effects on endothelial function, autonomic tone, inflammation, and improved risk factor control. The final common pathways of risk reduction presumably operate through improved endothelial function, leading to plaque passivation and thereby reducing the risk of recurrent ischemic events, as well as effects on autonomic control of cardiovascular function leading to a reduced risk of sudden cardiac death. Future work will be required to enhance our understanding, particularly of the antithrombotic potential of exercise training, which at this time remains unclear.

EXERCISE PRESCRIPTION

The main components of exercise prescription include the mode of exercise, the intensity, the frequency, and the duration (Table 32-1). To develop an individualized exercise training program, a complete risk stratification must be performed. Since post-ACS risk stratification is discussed elsewhere in this textbook, only the principal components of the pretraining risk stratification will be presented here. This topic is discussed in details in published guidelines.[75,76]

TABLE 32–1 Exercise Prescription for Subjects with Coronary Heart Disease

Aerobic Training
Intensity:*
• Heart rate: 65%-85% of maximal HR** or 40%-60% of the HR reserve (HR reserve = (maximal HR − resting HR) + resting HR).
• Gas exchange measurements: 40%-60% of maximal VO_2.
• Perceived exertion: Borg scale 12-14.
Frequency: 3-5 sessions/week.
Duration: 20-45 minutes/session.
Resistance Training
Intensity: 30%-40% of 1-RM for upper body exercises. 40%-60% of 1-RM for lower body exercises.
Repetitions: 10-15 per set.
Number of sets: 8-10 sets of different exercises.
Frequency: 2-3 sessions/week.

*As measured during a symptom-limited exercise test.

**See text if exercise-induced ischemia is present during the exercise test.

HR, heart rate; 1-RM, maximum weight that can be lifted to complete one repetition.

A symptom-limited exercise test[77] must be performed to evaluate exercise tolerance, perceived exertion (Borg scale), blood pressure and heart rate responses, as well as the presence or absence of exercise-induced angina, ischemia, and arrhythmias. An individualized Ramp protocol (treadmill or ergo cycle) is preferred since it provides a better estimation of exercise capacity[78] and can be better adapted to older patients or those with poor exercise capacity. An echocardiogram should be performed to evaluate left ventricular function, valvular abnormalities, presence of thrombus, etc.

Both aerobic (endurance) and resistance exercises are recommended.[76] For aerobic exercise, activities that use large muscle groups such as walking, jogging, running, swimming, and cycling are adequate.

Intensity

In general, exercise training should be undertaken at a moderate intensity. Several methods may be used to determine the target heart rate during exercise. The simplest one is to use 65% to 85% of the maximal heart rate achieved on the symptom-limited exercise test performed with the patient taking their usual medication including beta-blocking agents. A second method is to use 40% to 60% of the heart rate reserve (maximal heart rate – resting heart rate) and add this figure to the resting heart rate. For a patient with a maximal heart rate of 160 and a resting heart rate of 60, this would mean a target heart rate of 100 to 120 beats/min (160 – 60 × 40% – 60% + 60).

A third and more complex method since it necessitates the measurement of gas exchange during a cardiopulmonary exercise test, is to use a percentage (usually 40%-60%) of measured maximal oxygen uptake (VO_2).

Finally, exercise intensity may also be prescribed based upon the rate of perceived exertion measured with the Borg scale. This scale is used during the pretraining exercise test to specify the rate of perceived exertion during exercise training, and has been shown to be superior to the heart rate method for determining a precise exercise intensity.[79] This method also enables the patient to train at the desired intensity in many conditions where heart rate measurement is impractical (swimming, skiing, sailing, etc). The patient who uses the rate of perceived exertion to judge exercise intensity also learns to be aware of his or her symptoms and warning signs (chest pain, palpitations, dyspnea, etc.) rather than relying only on target heart rate. The 15-level original scale ranges from 6 (very light) to 20 (maximum) and the recommended target levels during training are 12 to 14. Level 14 on the Borg scale of perceived exertion generally corresponds to the ventilatory threshold, that is, the highest level of oxygen consumption during exercise in the absence of a significant increase in blood lactate.[79] Since it is not recommended for coronary patients to train above this threshold, the rating of perceived exertion on the Borg scale grade should be limited to 14 during training sessions.[76]

Patients with exercise-induced ischemia, that is, presenting a horizontal or downsloping ST-segment depression of greater than or equal to 1 mm, represent a special challenge for prescribing exercise intensity. Current recommendations state that in the presence of exercise-induced ischemia, the maximal heart rate during exercise training should be at least 10 beats per minute below the heart rate associated with greater than or equal to 1 mm ST-segment depression.[80] Unfortunately for patients with a relatively low ischemic threshold, this recommendation does not allow for a sufficient training stimulus.[81,82] Training coronary patients above the ischemic threshold when this threshold is relatively low is a controversial issue and requires medical supervision. Since 1991 at the Montreal Heart Institute Cardiovascular Prevention Centre, we have been prescribing exercise training in coronary patients at a target heart rate range of 65% to 85% of maximal achieved heart rate regardless of the presence or absence of exercise-induced ischemia. In 2002 we reported the chart review of 605 patients with documented coronary artery disease who trained from 3 months to 10 years representing a total of 295,000 patient-hours of training.[81] In this retrospective analysis, exercise training above the ischemic threshold was not associated with a higher incidence of documented coronary events relative to exercise training in the absence of exercise-induced ischemia. The event rate was 1/55,000 patient-hours of training versus 1/50,000 patient-hours, respectively. To evaluate the possibility of myocardial damage after a training session above the ischemic threshold, we measured troponin T levels in 20 patients with stable coronary disease after 2 training sessions: one above the ischemic threshold and the other under this threshold. We found no evidence of myocardial damage following either training session.[83]

The recommended frequency of training is between 3 and 5 sessions per week and the duration is usually from 20 to 45 minutes of continuous or discontinuous exercise. The exercise sessions must be preceded by a warm-up period of 5 to minutes and by an equivalent cool-down period.

Resistance Training

Resistance training, because its health benefits and safety are well documented, is now part of exercise-based CR[76,84] for stable coronary patients and for patients after an ACS.[85] Resistance training enhances muscular strength, endurance, and muscular mass. It also has beneficial effect on most CV risk factors. The prescription of resistance training is based on the maximum weight that can be used to complete one repetition (1-RM). The usual prescription is to perform 30% to 40% of 1-RM for upper body exercises and 40% to 60% of 1-RM for lower body exercises. Each set of exercises includes 10 to 15 repetitions, and usually 8 to 10 sets of different exercises are performed. The resistance training sessions are repeated 2 to 3 times per week.[86]

Risk of Exercise-Related Major Cardiac Events

The risk of cardiac events during exercise-based CR has been the subject of numerous studies. The reported range of major cardiac events is between 1/50,000 to 1/120,000 patient-hours of exercise in medically supervised programs.[80] In a recent publication, Pavy and colleagues[87] reported the data of a prospective registry of 65 CR programs in France representing 25,420 patients. During 1 year, the major cardiac event rate was 1/49,565 patient-hours of exercise training and the cardiac arrest rate was 1/1.3 million patient-hours of exercise. No deaths occurred during the 1-year period. Franklin and coworkers[88] reported a single center experience of 16 years of exercise-based CR. Two cardiac arrests and three nonfatal myocardial infarctions occurred. Accordingly, the rate of cardiac arrest was 1/146,127 per patient-hours of exercise and for acute myocardial infarction, the rate was 1/97,418 patient-hours of exercise. The authors concluded that the risk of major cardiovascular events during CR is very low and that current risk stratification criteria can identify patients at risk of exercise-related cardiovascular events.

Risk Stratification and Level of Supervision

Risk stratification after an ACS is discussed in Chapter 18. Risk stratification for exercise training in healthy individuals and in cardiac patients is also recommended.[12] Class A represents apparently healthy individuals. Patients with a recent ACS can be categorized as low risk (class B) or moderate to high risk (class C). In summary, class B patients have the following characteristics:

- New York Heart Association (NYHA) or Canadian Cardiovascular Society (CCS) class 1 to 2
- Exercise capacity ≥6 metabolic equivalents (METS)

- No clinical heart failure
- No angina or ischemia <6 METS
- Ejection fraction >30%

Class C patients present the following characteristics:

- NYHA or CCS class 3 to 4
- Exercise capacity <6 METS
- Angina or ischemia <6 METS
- Nonsustained ventricular tachycardia (VT)
- Ejection fraction <30%

Low-risk patients (class B) can safely train in a structured program but do not require direct medical supervision. They can also train at home with prior evaluation and instructions if they are capable of monitoring their exercise intensity by the rate of perceived exertion method or heart rate.

Moderate- to high-risk patients (class C) should be referred to a medically supervised program with all the necessary personnel and equipment. The personnel must be trained to provide advanced cardiac life support and defibrillation.

Air Pollution and Risk of Coronary Events During Exercise

A very large number of epidemiologic and experimental studies have demonstrated the link between atmospheric pollution and CV events.[89] Miller and coworkers studied the effect of particulate matter (less than 2.5 μm in aerodynamic diameter) exposure in 65,893 postmenopausal women initially free of previous CV disease in 36 U.S. cities during a mean follow-up of 6 years. They reported that each increase of 10 μg per cubic meter of particulate matter was associated with a 24% increase in the risk of a CV event and a 76% increase in the risk of CV-related death.[90] Short-term exposure to atmospheric particulate matter also significantly contributes to increased mortality and morbidity, especially in high-risk individuals.[91-93] Peters and colleagues showed that transient exposure to traffic may trigger an acute MI in high-risk individuals.[94] This is especially important for patients who exercise in cities with poor air quality. In a recent study of patients with prior MI exposed to diesel smoke during exercise, Mills and coworkers[95] demonstrated that diesel exhaust increases myocardial ischemia and inhibits endogenous fibrinolytic capacity. These findings suggest that the risk of triggering an acute coronary event may be increased when exercising in polluted areas, and some authors recommend avoiding exercise training near traffic when possible to "optimize the risk-benefit ratio" of exercise.[96] Potential mechanisms to explain the effect of poor air quality on triggering ACS include a reduction in myocardial oxygen supply secondary to vasoconstriction or a decrease in oxygen carrying capacity caused by increased carbon monoxide. Transient thrombus formation may also be involved since polluted environments with small particulate matter are proinflammatory and prothrombotic.[97]

CONCLUSION

Exercise training after ACS is a very effective nonpharmacologic intervention to reduce mortality and morbidity and also to improve quality of life. Its clinical benefits appear to be related to multiple cardioprotective mechanisms, including effects on endothelial function, autonomic tone, inflammation, and improved risk factor control. Unfortunately this therapeutic intervention is still greatly underused.

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SECTION V

A Structure-Based Perspective of the Modern CCU and Treatment Guidelines

CHAPTER 33

Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes: European Society of Cardiology Guidelines

Jean-Pierre Bassand and Christian W. Hamm

The European Society of Cardiology (ESC) published new guidelines for the management of non–ST-elevation acute coronary syndromes (NSTE-ACS) in June 2007.[1] This is the third edition of guidelines to be published on this topic; the first was published in 2000, and the second in 2003. Four years elapsed before this latest version was published, since there were few new developments that incited us to completely revise the NSTE-ACS guidelines. Therefore, the 2007 guidelines are not an update, but rather a whole new document, designed to take a fresh approach to the topic. The task force was composed of 11 members (10 Europeans and 1 American). The experts were selected according to their expertise in the field of cardiovascular disease, and especially acute coronary syndromes (ACS). One member of the task force was selected for his particular expertise in methodology, statistics, and meta-analysis methods.

The basic concept of the ESC panel was to provide a practical and patient-oriented document, which clinicians can use on a daily routine basis.

The task force members decided to adhere to some new basic principles in writing practice guidelines. This approach may explain why the European guidelines

differ in some aspects from the American Heart Association/American College of Cardiology (AHA/ACC) American guidelines on the same topic published two months later.[2] In particular, the European task force decided to give precedence to clinical trials that used contemporary treatments, such as pharmacologic environment including the aspirin, clopidogrel and glycoprotein (GP) IIb/IIIa inhibitors, and also revascularization strategies. Less weight was accorded to trials or meta-analyses including older studies in the field of NSTE-ACS where invasive strategy was not encouraged, or where a contemporary pharmacologic and interventional (e.g., stents) approach was not available.

Secondly, the panel took into account the methodologic quality of the clinical trials used for recommendations, giving priority to trials with adequate sample size, and disregarding trials with less robust endpoints, namely composite endpoints incorporating weak variables such as need for revascularization or other surrogate markers. Furthermore, double-blind trials were also given priority over open-label studies.

Lastly, the ESC task force particularly aimed to address some important practical issues that had never been addressed before in guidelines, such as bleeding and transfusion, and the problems posed by special populations (the elderly, females, patients with chronic kidney disease, or diabetes). In areas where evidence is lacking, it was tried to give practical recommendations such as assessment of resistance to antiplatelet therapy, association of vitamin K antagonists with dual antiplatelet therapy, etc.

Cost issues are usually not addressed in guidelines. Therefore it is a novel approach to introduce this in terms of number needed to treat (NNT) to prevent death or myocardial infarction for every treatment or procedure. This may give clinicians a clear idea of the benefit-risk ratio. Vice versa, the number needed to harm (NNH) provides a measure of the price to pay such as in terms of bleeding complications.

The present document is a summary of the official ESC guidelines, and for the purposes of conciseness, provides fewer details about the treatment effects of the different drugs and procedures proposed for the treatment of NSTE-ACS.

CARDIOVASCULAR DISEASE

Cardiovascular diseases are presently the leading causes of death in industrialized countries and expected to become so in emerging countries by 2020. Among these, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. The clinical presentations of ischemic heart disease include silent ischemia, stable angina pectoris, unstable angina (UA), myocardial infarction (MI), heart failure, and sudden death. Patients with chest pain represent a very large proportion of all acute medical hospitalizations in Europe. Distinguishing those with ACS within the very large proportion with suspected cardiac pain represents a diagnostic challenge, especially in those without clear symptoms or electrocardiographic features. In spite of current treatment, the rates of death, MI, and readmission of patients with ACS remain high.

It is well established that ACS in their different clinical presentations share a widely common pathophysiologic substrate. Pathologic, angioscopic, and biological observations have demonstrated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolization, resulting in myocardial underperfusion, represents the basic pathophysiologic mechanisms in most ACS.

As this is a life-threatening state of atherothrombotic disease, criteria for risk stratification have been developed to allow the clinician to make timely decisions on pharmacologic management as well as on coronary revascularization strategies, tailored to the individual patient. The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the electrocardiogram (ECG). Two categories of patients may be encountered: Patients with acute chest pain and persistent ST-segment elevation, and patients with acute chest pain but without persistent ST-segment elevation.

Patients with Typical Acute Chest Pain and Persistent (>20 Minutes) ST-Segment Elevation

This is termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop an ST-segment elevation MI (STEMI). The therapeutic objective is to achieve rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy.

Patients with Acute Chest Pain but Without Persistent ST-Segment Elevation

Patients without persistent ST-segment elevation have instead persistent or transient ST-segment depression or T wave inversion, flat T waves, pseudo-normalization of T waves, or no ECG changes at presentation. The initial strategy in these patients is to alleviate ischemia and symptoms, to monitor the patient with serial ECG, and to repeat measurements of markers of myocardial necrosis. At presentation, the working diagnosis of NSTE-ACS, based on the measurement of troponins, will be further qualified in non–ST-segment elevation MI (NSTEMI) or UA. In a certain number of patients, coronary artery disease will subsequently be excluded as cause of symptoms. The therapeutic management is guided by the final diagnosis.

Epidemiology and Natural History

The diagnosis of NSTE-ACS is more difficult to establish than STEMI and therefore its prevalence is harder to estimate. In addition, in recent years, a new definition of MI has been introduced to take into account the use of more sensitive and more specific biomarkers of cell death.[3,4] It has been shown from surveys that the annual incidence of hospital admissions for NSTE-ACS is in the range of 3 per thousand inhabitants. This rate varies widely in Europe, with considerably higher incidence in Central and Eastern Europe as compared with Western Europe. Over time, the rate of NSTE-ACS has increased gradually, whereas the rate of STEMI has decreased. Nowadays, NSTE-ACS represents a higher proportion of hospitalizations than STEMI.

Similarly, surveys have established that the prognosis of NSTE-ACS also varies considerably. The death rate is lower during the first 30 days than for STEMI, but at 1 year, the death rate is virtually the same in both conditions.

The implications for therapy are as follows:

- NSTE-ACS is more frequent than STEMI.
- In contrast to STEMI, where most events occur before or shortly after presentation, in NSTE-ACS these events continue over days and weeks.
- Mortality rates of STEMI and NSTE-ACS after 6 months are comparable.

This suggests that treatment strategies for NSTE-ACS need to address the requirements of the acute phase as well as longer-term treatment.

Pathophysiology

Atherosclerosis is a chronic, multifocal immunoinflammatory, fibroproliferative disease of medium-sized and large arteries mainly driven by lipid accumulation.[5] Symptomatic coronary lesions contain a variable mix of chronic atherosclerosis and acute thrombosis. Since the exact nature of the mix is unknown in the individual patient, the term *atherothrombosis* is frequently used. Generally, atherosclerosis predominates in lesions responsible for chronic

stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS.[6,7]

ACS represent a life-threatening manifestation of atherosclerosis usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiologic element. In rare cases, ACS may have a nonatherosclerotic etiology such as arteritis, trauma, dissection, thromboembolism, congenital anomalies, cocaine abuse, and complications of cardiac catheterization.

The Vulnerable Plaque

Atherosclerosis is not a continuous, linear process but rather a disease with alternate phases of stability and instability. Plaque rupture or plaque erosion are the two main underlying mechanisms in acute coronary syndromes. The plaques prone to instability and rupture have a large lipid core, a low density of smooth muscle cells, a high concentration of inflammatory cells, and a thin fibrous cap covering the lipid core as compared with stable plaques.

Coronary Thrombosis

Coronary thrombosis in ACS usually develops at the site of a vulnerable ruptured or eroded plaque. The thrombus is fibrin-rich and completely occlusive in STEMI, whereas it is platelet-rich and partially or intermittently occlusive in NSTE-ACS. A platelet-rich thrombus at the site of plaque rupture may fragment into small particles, which embolize downstream and may occlude arterioles and capillaries. These platelet emboli may cause small areas of necrosis in the myocardium.

The Vulnerable Patient

Multiple sites of plaque rupture with or without intracoronary thrombosis, along with elevated levels of various systemic markers of inflammation and thrombosis as well as coagulation system activation have been documented in patients with ACS. Hypercholesterolemia, tobacco smoking, and increased fibrinogen levels have been reported to contribute to instability in these patients, leading to thrombotic complications.

Endothelial Vasodilatory Dysfunction

Minor changes in coronary tone may greatly affect myocardial blood supply and thus cause insufficient flow at rest or during exercise. Vasospasm most frequently occurs at the site of atherosclerotic plaques in which local vasoconstricting substances, such as serotonin, thromboxane A_2, and thrombin are released locally by platelets and intracoronary thrombi. The prototype of dynamic coronary obstruction as a cause of ACS is Prinzmetal's variant angina, in which coronary vasospasm is the main determinant of an abrupt reduction in flow. This usually occurs at sites of critical or subcritical stenoses.

Secondary Mechanisms

A number of extracardiac mechanisms can cause a critical increase in myocardial oxygen consumption to above the supply threshold, such as fever, tachycardia, thyrotoxicosis, hyperadrenergic state, sudden emotional stress, and increased left ventricular (LV) afterload (hypertension, aortic stenosis).

Myocardial Injury

The myocardium may be normal or there may be varying degrees of necrosis. Focal myocardial necrosis was shown to be surrounded by areas of inflammation. In clinical practice this minor damage may be detected only by cardiac troponin T (cTnT) or troponin I (cTnI) elevations and are classified as MI according to the ESC/AHA/ACC Consensus Document. This concept is of clinical importance, because it has major practical implications with respect to short-term prognosis and the choice of the therapeutic regimen.

DIAGNOSIS AND RISK ASSESSMENT

Diagnosis and risk stratification are closely linked in ACS. Patients with NSTE-ACS are at high risk for MI, recurrence of MI, or death. Risk must not be understood in a binary way, but rather as a continuum from patients with very high risk to patients with low risk.

Clinical Presentation and History

The clinical presentation of NSTE-ACS encompasses a wide variety of symptoms. Traditionally, several clinical presentations have been distinguished:

- Prolonged (>20 minutes) anginal pain at rest.
- New onset (de novo) severe angina (class III of the Classification of the Canadian Cardiovascular Society (CCS).
- Recent destabilization of previously stable angina with at least CCS class III angina characteristics (crescendo angina).
- Or post-MI angina.

Prolonged pain is observed in 80% of patients, while de novo or accelerated angina are observed in only 20%.

In patients with intermittent symptoms, an increasing number of episodes preceding the index event may also have an impact on outcome. The presence of tachycardia, hypotension, or heart failure upon presentation indicates a poor prognosis and needs rapid diagnosis and management. It is important to identify clinical circumstances that may exacerbate or precipitate NSTE-ACS, such as anemia, infection, inflammation, fever, and metabolic or endocrine (in particular thyroid) disorders.

Diagnostic Tools

Physical Examination. The physical examination is frequently normal. Signs of heart failure or hemodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. An important goal of the physical examination is to exclude noncardiac causes of chest pain, and nonischemic cardiac disorders.

Electrocardiogram. The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected NSTE-ACS. It should be obtained within 10 minutes after first medical contact upon arrival of the patient in the emergency room and immediately interpreted by a qualified physician. The findings range from normal ECG (observed in 5% of proven NSTE-ACS) to T wave inversion or ST depression. Depending on the number of leads where it is observed and its magnitude, ST depression has a strong prognostic implication.[8] The prognostic implication of T wave inversion is less severe than for ST depression.

Continuous ST-Segment Monitoring. On-line continuous computer-assisted 12-lead ST-segment monitoring is a valuable diagnostic tool. Several studies revealed that 15% to 30% of patients with NSTE-ACS have transient episodes of ST-segment changes, predominantly ST-segment depression. ST-monitoring adds independent prognostic information to the ECG at rest, troponins, and other clinical parameters.

Exercise or Other Stress Testing. In patients who continue to have typical ischemic rest pain, no stress test should be performed. However, a stress test has a predictive value and is therefore useful before discharge in patients with nondiagnostic ECG provided there is no pain, no signs of heart failure, and normal biomarkers (repeat testing).

Biochemical Markers

Several biomarkers have been investigated in recent years to be used for diagnostic and risk stratification. These reflect different pathophysiologic aspects of NSTE-ACS, such as minor myocardial cell injury, inflammation, platelet activation, or neurohormonal activation. For the long-term prognosis, indicators of LV and renal dysfunction or diabetes play also an important role.

Markers of Myocardial Injury. Troponin T (cTnT) or cTnI are the preferred markers of myocardial injury, because they are more specific and more sensitive than the traditional cardiac enzymes such as creatine kinase (CK) or its isoenzyme MB (CK-MB). They reflect irreversible myocardial cellular necrosis resulting from distal embolization of platelet-rich thrombi from the site of a ruptured or eroded plaque. Troponins are the best biomarker to predict short and long term outcome with respect to MI and death.[9,10] They are also useful for selecting appropriate treatment in patients with NSTE-ACS. An initial rise in troponins in peripheral blood occurs after 3 to 4 hours. Troponin levels may be persistently elevated for up to 2 weeks; this is caused by proteolysis of the contractile apparatus. Minor or moderate elevations of troponins appear to carry the highest early risk in patients with NSTE-ACS.

A single negative test for troponins on arrival of the patient in hospital is not sufficient for ruling out, as in many patients troponin rise can be detected only in the subsequent hours. In order to demonstrate or to exclude myocardial damage, repeated blood sampling and measurements are required 6 to 12 hours after admission and after any further episodes of severe chest pain. A second sample in the absence of any other suspicious findings may be omitted only if the patient's last episode of chest pain was more than 12 hours prior to the initial determination of troponins. Elevation of troponins can be observed in many other clinical circumstances, but do not truly reflect myocardial infarction in the absence of clinical symptoms of ischemia and obstructive coronary artery disease. Differential diagnosis can be difficult. The conditions that are associated with troponin release have been summarized elsewhere.[4] In brief, troponins can be elevated in the following conditions: (1) severe congestive heart failure; (2) aortic dissection; (3) cardiac contusion (ablation, pacing); (4) myocarditis, endocarditis or pericarditis; (5) hypertensive crisis; (6) tachyarrhythmias or bradyarrhythmias; (7) pulmonary embolism; (8) apical ballooning syndrome; (9) chronic or acute renal dysfunction; (10) acute neurologic disease, including stroke or subarachnoid hemorrhage; (11) drug toxicity (e.g., Adriamycin, 5-fluorouracil, Herceptin); (12) snake venoms; (13) burns if affecting more than 30% of body surface area; (14) rhabdomyolysis; and (15) critically ill patients, especially with respiratory failure, or sepsis.

This means that the diagnosis of NSTE-ACS should never be made only on the basis of cardiac biomarkers whose elevation should be interpreted in the context of other clinical findings.

Markers of Inflammatory Activity. Of the numerous inflammatory markers that have been investigated over the past decade, C-reactive protein measured by high sensitive assays (hsCRP) is the most widely studied and linked to higher rates of adverse events. There is robust evidence that even among patients with troponin-negative NSTE-ACS, elevated levels of hsCRP are predictive of long-term mortality (>6 months).[11]

Markers of Neurohumoral Activation. Natriuretic peptides, like brain type (B-type natriuretic peptide [BNP]) or its N-terminal prohormone fragment (NT-proBNP) are highly sensitive and fairly specific markers for the detection of LV dysfunction. There is robust retrospective data in NSTE-ACS showing that patients with elevated BNP or NT-proBNP levels have a 3-fold to 5-fold increased mortality rate as compared with those having lower levels.[12] The level is strongly associated with the risk of death even when adjusted for age, Killip class, and LV ejection fraction (LVEF). However, they are markers of long-term prognosis, but have limited value for initial risk stratification and hence for selecting the initial therapeutic strategy in NSTE-ACS.

Markers of Renal Function. Impaired renal function is a strong independent predictor for long-term mortality in ACS patients.[13] Long-term mortality is influenced by the degree of renal function, as it increases exponentially with decreasing glomerular filtration rate/creatinine clearance (GFR/CrCl). As compared with patients with normal renal function, the odds ratio (OR) for death at 1 year was 1.76 for mild renal dysfunction, 2.72 for moderate renal dysfunction, and 6.18 for severe renal dysfunction.

Multimarker Approach

Currently, it is recommended to use troponins (cTnT or cTnI) for the acute risk stratification on arrival of the patient in the hospital. At the same time or during the subsequent days CrCl and BNP or NT-proBNP allow the estimation of any renal or myocardial dysfunction with their inherent impacts on treatment and long-term outcome.[14] Currently only hsCRP is available on a routine basis for the detection of the underlying inflammatory activity responsible for long-term mortality.

Echocardiography and Noninvasive Myocardial Imaging

Echocardiography is an important tool to quantify LV function, and rule out differential diagnoses. Other noninvasive tools can be useful for the same purposes. Aortic stenosis, aortic dissection, pulmonary embolism, or other conditions can mimic ACS and can be ruled out with echocardiography. Magnetic resonance imaging (MRI) is a valuable alternative to echocardiography.

Imaging of the Coronary Anatomy. The gold standard is still conventional invasive coronary angiography.

Patients with multiple vessel disease as well as those with left main stenosis are at highest risk of serious cardiac events. Angiographic assessment of the characteristics and location of the culprit lesion as well as other lesions is essential if revascularization is being considered. At the current state of development, cardiac computed tomography (CT) cannot be recommended as coronary imaging modality in NSTE-ACS, because of suboptimal diagnostic accuracy.

MRI is not established as an imaging tool for coronary arteries. It may only be useful in the course of hospitalization in quantifying myocardial injury or excluding myocarditis. CT or MRI may, however, be indicated for evaluation of differential diagnoses, such as pulmonary embolism or aortic dissection.

Differential Diagnoses

Several cardiac and noncardiac conditions may mimic NSTE-ACS. Some are cardiac, vascular, or pulmonary conditions such as myocarditis, pericarditis, myopericarditis, cardiomyopathy, apical ballooning (Tako-Tsubo syndrome), pulmonary embolism, pulmonary infarction, pneumonia, pneumothorax, aortic dissection, aortic aneurysm, and aortic coarctation. Other conditions may also mimic the clinical scene of ACS, with gastrointestinal causes including esophageal spasm, esophagitis, peptic ulcer, pancreatitis, cholecystitis, or orthopedic/traumatic causes such as cervical discopathy, rib fracture, muscle injury/inflammation, costochondritis, or even hematologic causes such as sickle cell anemia.

Risk Scores

Several risk stratification scores have been developed and validated in large patient populations. In clinical practice only simple risk scores are useful.

The GRACE risk scores[15] are based upon a large unselected population of an international registry of full spectrum of ACS patients. The risk factors were derived with independent predictive power for in-hospital deaths and postdischarge deaths at 6 months. Based on direct comparisons, the GRACE risk score is recommended as preferred classification to apply on admission and at discharge in daily clinical routine practice.

Other risk scores have been developed (e.g., the TIMI and PURSUIT risk scores).

Recommendations for Diagnosis and Risk Stratification

- Diagnosis and *short-term* risk stratification of NSTE-ACS should be based on a combination of clinical history, symptoms, ECG, biomarkers and risk score results (I-B).
- The evaluation of the individual risk is a dynamic process that is to be updated as the clinical situation evolves.
  - A 12-lead electrocardiogram (ECG) should be obtained within 10 minutes after first medical contact and immediately read by an experienced physician. (I-C) Additional leads (V_{3R} and V_{4R}, V_7-V_9) should be recorded. ECG should be repeated in case of recurrence of symptoms, and at 6 hours, 24 hours, and before hospital discharge (I-C)
  - Blood must be drawn promptly for troponin (cTnT or cTnI) measurement. The result should be available within 60 minutes. (I-C) The test should be repeated after 6 to 12 hours if the initial test is negative (I-A)
  - Established risk scores (such as GRACE) should be implemented for initial and subsequent risk assessment (I-B)
  - An echocardiogram is recommended to rule in or out differential diagnoses (I-C)
  - In patients without recurrence of pain, normal ECG findings, and negative troponin tests, a noninvasive stress test for inducible ischemia is recommended before discharge (I-A)
- The following predictors of *long-term* death or MI should be considered in risk stratification (I-B):
  - *Clinical indicators*: age, heart rate, blood pressure, Killip class, diabetes, previous MI/CAD
  - *ECG markers:* ST-segment depression
  - *Laboratory markers:* troponins, GFR/CrCl/Cystatin C, BNP/NT-proBNP, hsCRP
  - *Imaging findings:* low ejection fraction, main stem lesion, three-vessel disease.
  - *Risk score result*

TREATMENT

The treatment options described in this section are based on evidence from numerous clinical trials or meta-analyses.

Four categories of acute treatment are discussed: anti-ischemic agents, anticoagulant, antiplatelet agents, and coronary revascularization. Generally, the therapeutic approach is based on whether the patient is to be only medically treated, or in addition referred to angiography and revascularization. Many of the treatment options were evaluated more than two decades ago or tested only in specific subsets of patients. The recommendations take these circumstances into account.

Anti-Ischemic Agents

Anti-ischemic drugs decrease myocardial oxygen consumption (decreasing heart rate, lowering blood pressure, or depressing LV contractility) and/or induce vasodilatation.

Beta Blockers

A meta-analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to STEMI. Although no significant effect on mortality in NSTE-ACS has been demonstrated in these relatively small trials, the results may be extrapolated from larger randomized trials of beta blockers in patients with unselected MI.

Nitrates

Studies of nitrates in unstable angina have been small and observational. In patients with NSTE-ACS who require hospital admission, intravenous nitrates may be considered in the absence of contraindications. The dose should be titrated upward until symptoms (angina and/or dyspnea) are relieved unless side effects (notably headache or hypotension) occur.

Calcium Channel Blockers

From meta-analyses, no significant effect on death and nonfatal MI has been shown with the use of calcium channel blockers. On the contrary, observational studies suggest that short-acting nifedipine might be associated with a dose-dependent detrimental effect on mortality in patients with coronary artery disease. There is evidence that diltiazem might be beneficial in NSTEMI. Calcium channel blockers, particularly dihydropyridines, are the drugs of choice in vasospastic angina.

New Drugs

New antianginal drugs with different modes of action have been investigated in recent years. Only ranolazine, which exerts antianginal effects by metabolic mechanisms, was tested in a large ACS trial, but was not effective in reducing major cardiovascular events.

Recommendations for Anti-Ischemic Drugs

- Beta blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia. (I-B)
- Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes. (I-C)
- Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta blockers; they are useful in patients with contraindications to beta blockade, and in the subgroup of patients with vasospastic angina. (I-B)
- Nifedipine, or other dihydropyridines, should not be used unless combined with beta blockers. (III-B)

Anticoagulants

Anticoagulants are used in the treatment of NSTE-ACS to inhibit thrombin generation, thombin activity, or both, thereby reducing thrombus-related events. There is clear evidence that anticoagulation is effective in addition to platelet inhibition and that the combination of the two is more effective than either treatment alone.[16] With all anticoagulants, there is an increased risk of bleeding. The risk factors for bleeding are well defined. Several anticoagulants, which act at different levels of the coagulation cascade, have been investigated in NSTE-ACS:

- Unfractionated heparin (UFH) as intravenous infusion
- Low–molecular-weight heparin (LMWH) as subcutaneous injection
- Fondaparinux as subcutaneous injection every 24 hours
- Direct thrombin inhibitors (DTI) as intravenous infusion
- Vitamin-K antagonists (VKA) as oral medication

Unfractionated Heparin[17]

A pooled analysis of six trials testing short-term UFH versus placebo or untreated controls showed a significant 33% risk reduction for death and MI (OR, 0.67; 95% confidence interval [CI], 0.45-0.99; $P = .045$).[18] The risk reduction for MI accounted for practically all of the beneficial effect. When the data from FRISC, which compared LMWH to placebo, are added to this pooled analysis, then the risk reduction is even greater. In trials comparing the combination of UFH plus aspirin versus aspirin alone in NSTE-ACS, a trend toward a benefit was observed in favor of the UFH-aspirin combination, but at the cost of an increase in the risk of bleeding. Recurrence of events after interruption of UFH explains why this benefit is not maintained over time, unless the patient is revascularized before the interruption of UFH.[18,19]

Low–Molecular-Weight Heparin (LMWH)[18,19]

Several LMWHs are available for the treatment of patients with NSTE-ACS. Dalteparin and nadroparin were shown to be equally efficacious and safe as UFH in aspirin-treated patients. Enoxaparin has been compared with UFH in several trials. A meta-analysis of these trials totaling 21,946 patients showed no significant difference between the two compounds for death at 30 days, but a significant reduction in the combined endpoint of death and MI in favor of enoxaparin versus UFH (10.1% vs. 11.0%; OR, 0.91; 95% CI, 0.83-0.99). In this analysis, no significant difference was observed in the rate of bleeding or blood transfusion. The SYNERGY study was the most recent trial to compare enoxaparin to UFH.[20] It incorporated 10,027 high-risk patients planned for early invasive evaluation and revascularization. This trial used contemporary treatment, with extensive use of stents, GP IIb/IIIa inhibitors, and clopidogrel. Almost half of the patients included in the trial were submitted to percutaneous coronary intervention (PCI) or other forms of revascularization. No significant difference was observed in terms of death and MI at 30 days, but an excess of bleeding occurred with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% vs. 7.6%, $P = .08$), but a nonsignificant excess in GUSTO severe bleeding and transfusion.

LMWH, particularly enoxaparin, was used in combination with aspirin and thienopyridines, as well as GP IIb/IIIa inhibitors without safety concerns.

Factor-Xa Inhibitor (Fondaparinux)

The only selective factor-Xa inhibitor available for clinical use is fondaparinux. This is a synthetic pentasaccharide that exerts a selective antithrombin mediated inhibition of factor-Xa, resulting in a dose-dependent inhibition of thrombin generation without inhibition of the thrombin molecule per se.

Fondaparinux was compared to enoxaparin in a large trial incorporating 20,078 patients with NSTE-ACS, namely the OASIS-5 study.[21] Fondaparinux was used at a dose of 2.5 mg subcutaneous once daily, versus subcutaneous enoxaparin 1 mg/kg twice daily for 8 days maximum. At 9 days, there was no significant difference in the rate of primary endpoint (death, MI, or refractory ischemia) but there was a significant, 48% reduction of major bleeding. At 1 month, there was a significant reduction in death, which was sustained at 12 months. It was shown from further analysis that most of the beneficial effect observed in the risk reduction for death was linked to the reduction in bleeding. An excess of catheter thrombus during PCI was observed in the fondaparinux group as compared with the enoxaparin group (0.9% vs. 0.4%, $P = .001$). However, catheter thrombus was abolished over the duration of the trial by using a single bolus of UFH, added to fondaparinux in patients submitted to PCI without increasing bleeding risk.

Direct Thrombin Inhibitors (DTI)

Direct thrombin inhibitors bind directly to thrombin (factor IIa) and thereby inhibit thrombin-induced conversion of fibrinogen into fibrin. No significant beneficial effects were observed, but a higher bleeding rate was elicited from meta-analysis of the early trials carried out with direct thrombin inhibitors. The most recent trial, ACUITY, used bivalirudin and randomized 13,819 patients with moderate to high risk NSTE-ACS planned for invasive strategy[22] to three arms in an open-label design (conventional anticoagulant plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, bivalirudin alone). The primary endpoint was composite of ischemic events and bleeding complications. There was no significant difference, either in terms of efficacy or safety, between conventional anticoagulants plus GP IIb/IIIa inhibitors, and bivalirudin plus GP IIb/IIIa inhibitors. There was a significant risk reduction for bleeding with bivalirudin alone compared with a combination of conventional anticoagulants plus GP IIb/IIIa inhibitors, at the cost of a nonsignificant excess of ischemic events. The risk reduction of bleeding in ACUITY did not translate into a risk reduction for death at 30 days and 6 months. The treatment effects were consistent in all subgroups, except in patients who were not pretreated with clopidogrel before being submitted to PCI. Some criticisms have been leveled at this study since its publication because of a rather liberal margin of noninferiority used in the design of the trial.

Vitamin-K Antagonists (VKA)

In the current era of combining aspirin with clopidogrel in NSTE-ACS, VKA are mostly used in the presence of other indications for anticoagulation, such as atrial fibrillation or after implantation of a mechanical heart valve.

Based on experiences from clinical practice, it seems that antiplatelet and VKA combinations lead to only modest increases in bleeding risk in elderly patients, provided tight control of international normalized ratio (INR) can be obtained. In patients with active VKA treatment presenting with ACS, initiation of the anticoagulants recommended during the acute phase (UFH, LMWH, fondaparinux, or bivalirudin) should be withheld as long as the INR is not known and not started before the INR is less than 2.0. Reversal of anticoagulation with vitamin K supplements is not recommended unless necessary for bleeding complications.

Anticoagulants During Percutaneous Coronary Intervention Procedures in Non–ST-Segment Elevation Acute Coronary Sydrome

The use of platelet inhibition with aspirin and systemic anticoagulation with UFH has been the standard of care for PCI from the beginning. The current recommendation, based on empiric evidence, is to give UFH as an intravenous bolus of 100 IU/kg or 50 to 60 IU/kg if GP IIb/IIIa inhibitors are given. The efficacy of UFH is monitored by activated clotting time (ACT). However, the relation between ACT and the rate of clinical events, and the real utility of ACT monitoring remains controversial.

Bivalirudin during PCI procedures was tested in comparison to UFH/LMWH or bivalirudin plus GP IIb/IIIa inhibitors in the ACUITY trial. As already mentioned, a significant risk reduction for bleeding was observed with bivalirudin alone as compared to UFH/LMWH or bivalirudin with GP IIb/IIIa inhibitors, but with a significantly higher rate of ischemic events in patients not pretreated with clopidogrel.

Enoxaparin (1 mg/kg twice daily) was compared to UFH as antithrombotic agent in a PCI setting in 4687 NSTE-ACS in the SYNERGY trial. There was no difference in outcome during or after PCI, regardless of the drug used in the catheterization laboratory (UFH or enoxaparin). However, there was a strong trend toward an excess of bleeding (non–coronary

artery bypass grafting [CABG]-related TIMI major bleeds) with enoxaparin, as compared with UFH, possibly augmented by post-randomization crossover antithrombotic therapy. A recent trial (STEEPLE) involving 3258 patients undergoing elective PCI, suggests that lower doses of enoxaparin may be favorable with respect to bleeding.[23]

Enoxaparin and fondaparinux were compared in the setting of PCI in 6239 patients in OASIS-5.[21] Fondaparinux resulted in a lower risk of vascular access site complications as compared with enoxaparin and also in a lower risk of periprocedural complications (death, MI, stroke, and major bleeding). Catheter thrombus formation occurred more frequently with fondaparinux as compared with enoxaparin. Until new data are available, a standard dose of UFH (50-100 IU/kg bolus) is needed in addition to fondaparinux at the time of PCI, if fondaparinux was initiated prior to the procedure.

Recommendations for Anticoagulation

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy (I-A)
- Anticoagulation should be selected according to the risk of both ischemic and bleeding events (I-B)
- Several anticoagulants are available, namely UFH, LMWH, fondaparinux, and bivalirudin. The choice depends on the initial strategy (see section on Management Strategy: urgent invasive, early invasive, or conservative strategies) (I-B)
- In an urgent invasive strategy UFH (I-C), or enoxaparin (IIa-B) or bivalirudin (I-B) should be immediately started.
- In a nonurgent situation, as long as decision between early invasive or conservative strategy is pending:
  - Fondaparinux is recommended on the basis of the most favorable efficacy and safety profile (I-A)
  - Enoxaparin with a less favorable efficacy and safety profile than fondaparinux should be used only if the bleeding risk is low (IIa-B)
  - As the efficacy and safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux (IIa-B)
- At PCI procedures the initial anticoagulant should be maintained also during the procedure regardless whether this treatment is UFH (I-C), enoxaparin (IIa-B) or bivalirudin (I-B), while addititional UFH in standard dose (50-100 IU/kg bolus) is necessary in case of fondaparinux (IIa-C)
- Anticoagulation can be stopped within 24 hours after invasive procedure (IIa-C). In a conservative strategy, fondaparinux, enoxaparin, or other LMWH may be maintained up to hospital discharge (I-B)

Antiplatelet Agents

Platelet activation plays a key pathophysiologic role in NSTE-ACS.[24] Three related, but complementary strategies provide effective antiplatelet therapy: cyclooxygenase-1 inhibition (COX-1; aspirin), inhibition of ADP-mediated platelet aggregation with thienopyridines (ticlopidine and clopidogrel), and GP IIb/IIIa inhibition (tirofiban, eptifibatide, abciximab).

Acetylsalicylic Acid (Aspirin)

In a meta-analysis, aspirin was shown to lead to a 46% reduction in the rate of vascular events in the setting of NSTE-ACS.[24] No dose relation was observed in terms of efficacy. Doses ranging from 75 to 150 mg of aspirin were shown to be as effective as higher doses, but resulted in fewer bleeding complications.

Thienopyridines

Ticlopidine and clopidogrel are both adenosine diphosphate (ADP) receptor antagonists, which block the ADP-induced pathway of platelet activation by specific inhibition of the purinergic G protein–coupled P2Y 12 (P2Y12) ADP receptor. Ticlopidine has been shown to significantly reduce the risk of death and MI at 6 months in NSTE-ACS. However, clopidogrel is now more frequently used than ticlopidine due to better tolerability. In the CURE trial, clopidogrel was shown to lead to a 20% risk reduction for the composite endpoint of death from cardiovascular causes, nonfatal MI, or stroke (9.3% vs. 11.4%; risk ratio [RR], 0.80; 95% CI, 0.72-0.90; $P < .001$), but achieved at the cost of a higher bleeding risk (3.7% vs. 2.7%, RR, 1.38; 95% CI, 1.13-1.67; $P = .001$). However, there was no significant increase in life-threatening and fatal bleeds.[25] In the CURE study, the efficacy of clopidogrel was consistent throughout all subgroups, irrespective of the initial risk. A trend toward an excess of bleeding was observed in patients submitted to CABG, in whom clopidogrel was withdrawn less than 5 days before surgery.

Recommendations for Oral Antiplatelet Drugs

- Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication at an initial loading dose of 160 to 325 mg (nonenteric) (I-A), and at a maintenance dose of 75 to 100 mg long-term (I-A).
- For all patients, immediate 300-mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).
- For all patients with contraindication to aspirin, clopidogrel should be given instead (I-B).
- In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (IIa-B).
- In patients pretreated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible (IIa-C).

Glycoprotein IIb/IIIa Receptor Inhibitors (GP IIb/IIIa Inhibitors)

Three GP IIb/IIIa inhibitors have been approved for clinical use, namely abciximab, eptifibatide, and tirofiban. They block the final common pathway of platelet activation by binding to the fibrinogen and, under high shear conditions, to the von Willebrand factor, and thus inhibiting the bridging between activated platelets. Abciximab is a monoclonal antibody fragment, eptifibatide is a cyclic peptide, and tirofiban a peptidomimetic inhibitor. Clinical studies with oral GP IIb/IIIa inhibitors were stopped because of an excess of ischemic events, an excess of bleeding, or both. The results obtained with the use of GP IIb/IIIa inhibitors differed according to whether their use was associated with a conservative or an invasive strategy.[26]

Glycoprotein IIb/IIIa Receptor Inhibitors in a Conservative Strategy

A meta-analysis including 31,402 NSTE-ACS patients treated in clinical trials using GP IIb/IIIa inhibitors showed a 9% significant risk reduction for death and MI at 30 days (11.8% vs. 10.8%; OR, 0.91; 95% CI, 0.84-0.98; $P = .015$).[26] GP IIb/IIIa inhibitors were associated with an increase in major bleeding complications. They were shown to be particularly effective in diabetics, patients with ST depression and troponin-positive patients.

Abciximab. Abciximab was tested in the GUSTO-4-ACS trial[27] and did not show any superiority compared with the control group.

Eptifibatide. In the PURSUIT trial,[28] which included 10,948 patients, eptifibatide led to a significant reduction of the 30-day composite endpoint of death or nonfatal MI (14.2 vs. 15.7%, eptifibatide vs. placebo; $P = .04$), but at the cost of an increase in the risk of TIMI major bleeding (10.6 vs. 9.1%; $P = .02$); however, there was no excess of intracranial bleeding.

Tirofiban. Tirofiban has been tested in two trials.[29,30] In the PRISM trial, there was a significant risk reduction for the composite endpoint of death, MI, or refractory ischemia at 48 hours and 30 days, but this was not maintained in the long term. In the PRISM-PLUS trial, a significant reduction of the risk of death, MI, and refractory ischemia was obtained at 7 days (12.9% vs. 17.9%; RR, 0.68; 95% CI, 0.53-0.88; $P = .004$) and maintained at 30 days and 6 months in the tirofiban plus UFH group, as compared with UFH alone. Major bleeds (according to the TIMI criteria) were not statistically more frequent in the tirofiban group, despite a trend toward an increase (1.4% vs. 0.8%; $P = .23$).

Glycoprotein IIb/IIIa Receptor Inhibitors in an Invasive Strategy

Consistent results have been obtained in three different meta-analyses exploring the impact of the use of GP IIb/IIIa inhibitors in the setting of PCI. Two meta-analyses showed that a significant risk reduction for death and MI at 30 days could be achieved when GP IIb/IIIa inhibitors were administered before taking patients to the catheterization laboratory, and maintained during PCI.[31] Kong and colleagues reported a significant risk reduction in 30 day mortality among a total of 20,186 patients (0.9% vs. 1.3%; OR, 0.73; 95% CI, 0.55-0.96; $P = .024$). Importantly, thienopyridines and stents were not routinely used in these trials.

Abciximab. The most recent trial with abciximab in this setting is ISAR-REACT 2, in which 2022 high-risk NSTE-ACS patients were randomized to dual antiplatelet therapy (aspirin or clopidogrel) or to triple antiplatelet therapy (abciximab in addition to aspirin and clopidogrel).[32] The 30-day composite endpoint of death, MI, or urgent target vessel revascularization (TVR) occurred significantly less frequently in abciximab-treated patients versus placebo (8.9% vs. 11.9%; RR, 0.75; 95% CI, 0.58-0.97; $P = .03$). Triple antiplatelet therapy was efficacious only in troponin-positive patients.

Eptifibatide. Eptifibatide showed superiority over placebo in the ESPRIT trial.[33] In this trial, a significant reduction in the risk of death, MI, urgent TVR, and bail-out use of GP IIb/IIIa inhibitors was demonstrated at 48 hours, and maintained at 30 days, and at 6 months (6.6% vs. 10.5%; RR, 0.63; 95% CI, 0.47-0.84; $P = .0015$ at 48 hours) for eptifibatide versus placebo.

Tirofiban. In the TARGET study,[34] tirofiban was shown to be inferior to abciximab possibly related to an inadequate dose. Newer, but smaller studies with higher bolus doses revealed a more potent antiplatelet effect.

Adjunctive Therapy

Several trials have shown that LMWH, particularly enoxaparin, can be safely used with GP IIb/IIIa inhibitors, without compromising efficacy. It should be noted that most of the trials carried out with GP IIb/IIIa inhibitors were performed before clopidogrel was made available. However, ISAR-REACT 2 showed that triple antiplatelet therapy, associating aspirin, clopidogrel and abciximab, may lead to better outcome in high-risk NSTE-ACS patients submitted to PCI.[32]

Bivalirudin and UFH/LMWH were shown to have equivalent safety and efficacy when used with triple antiplatelet therapy, including GP IIb/IIIa inhibitors in the ACUITY trial. However, bivalirudin alone was associated with a lower bleeding risk as compared with any combination with GP IIb/IIIa inhibitors.[22]

Recommendations for Glycoprotein IIb/IIIa Inhibitors

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment are recommended in addition to oral antiplatelet agents (IIa-A).
- The choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischemic and bleeding events (I-B).
- Patients who received initial treatment with eptifibatide or tirofiban prior to angiography, should be maintained on the same drug during and after PCI (IIa-B).
- In high-risk patients not pretreated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography. (I-A) The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).
- GP IIb/IIIa inhibitors must be combined with an anticoagulant (I-A).
- Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH (IIa-B).
- When anatomy is known and PCI planned to be performed within 24 hours with GP IIb/IIIa inhibitors, most secure evidence is for abciximab (IIa-B).

Resistance to Antiplatelet Agents or Drug Interactions

Resistance to antiplatelet agents describes partial or total failure of an antiplatelet agent to achieve the expected inhibition of platelet function and would therefore be better named low- or hyporesponsiveness. The term refers to the variability in the magnitude of platelet aggregation inhibition measured ex vivo achieved in a population of treated patients. The magnitude of true resistance to antiplatelet agents remains poorly defined. No simple test has been reliably validated to assess the level of platelet function inhibition for any antiplatelet agent used in atherothrombosis.[35] Resistance to antiplatelet agents was shown to lead to an increased risk of ischemic events. Drug interactions may also compromise the efficacy or safety of some drugs used in NSTE-ACS.

Resistance to aspirin has been identified in one substudy of the HOPE trial, in which different degrees of thromboxane A_2 inhibition were associated with a significant difference in rate of events.[36] The variability in response observed with clopidogrel is probably linked to the variability in the two different steps of liver metabolism required to transform clopidogrel, which is a prodrug, into its active compound. There have been attempts to overcome this problem by raising the dose of clopidogrel. New ADP receptor antagonists are currently under clinical investigation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to interact negatively with aspirin. A higher rate of events after NSTE-ACS has been observed in patients treated with NSAIDs. No formal interaction has been described with clopidogrel. However, the association of clopidogrel with vitamin K antagonists is not recommended, since it may potentially increase bleeding.

Recommendations for Resistance to Antiplatelet Treatment or Drug Interactions

- Routine assessment of platelet aggregation inhibition in patients submitted to either aspirin or clopidogrel therapy, or both, is not recommended (IIb-C).

- NSAID (selective COX 2 inhibitors and nonselective NSAIDs) should not be administered in combination with either aspirin or clopidogrel (III-C).
- Clopidogrel can be administered with all statins (I-B).
- The triple association of aspirin, clopidogrel, and VKA should only be given if compelling indication exists, in which case, the lowest efficacious INR and shortest duration for the triple association should be targeted (IIa-C).

Withdrawal of Antiplatelet Agents

Interruption of dual antiplatelet therapy soon after the acute phase of NSTE-ACS may expose patients to a high risk of recurrence of events, especially after stent implantation. If interruption of antiplatelet agents is necessary because of major bleeding or need for urgent surgery, for example, no alternative treatment can be proposed as a substitute. Temporary interruption of dual antiplatelet therapy is discouraged. Caution must be exercised when planning stent implantation. It is recommended to avoid drug-eluting stents in patients who may require urgent surgery in the short term.

Recommendations for Withdrawal of Antiplatelet Treatment

- Temporary interruption of dual antiplatelet therapy (aspirin and clopidogrel) within the first 12 months after the initial episode is discouraged (I-C).
- Temporary interruption for major or life-threatening bleeding or for surgical procedures where even minor bleeding may result in severe consequences (brain or spinal surgery) is mandatory (IIa-C).
- Prolonged or permanent withdrawal of aspirin, clopidogrel or both is discouraged unless clinically indicated. Consideration should be given to the risk of recurrence of ischemic events which depends (among other factors), on initial risk, on presence and type of stent implanted, and on time window between proposed withdrawal and index event and/or revascularization (I-C).

Coronary Revascularization

Revascularization for NSTE-ACS is performed to relieve angina and ongoing myocardial ischemia, and to prevent progression to MI or death. The indications for myocardial revascularization and the preferred approach (PCI or CABG) depend on the extent and severity of the lesions as identified by coronary angiography, the patient's condition, and comorbidity.

Coronary Angiography

Invasive coronary angiography remains pivotal in determining suitability for percutaneous and/or surgical revascularization. In hemodynamically compromised patients (pulmonary edema, hypotension, severe life-threatening arrhythmias), it may be advisable to perform the examination after placement of an intra-aortic balloon pump, to limit the number of coronary injections and to omit left ventricular angiography.

Invasive Versus Conservative Strategy

Several meta-analyses have been performed on all trials that aimed to compare invasive versus conservative strategies in the setting of NSTE-ACS. With all the limitations linked to different definitions of endpoints, and due to the fact that many of the trials were not contemporary (no stents, no GP IIb/IIIa inhibitors, no clopidogrel), it has consistently been shown that invasive strategy followed by revascularization leads to an excess of events during the first month of evolution, but derives better long-term benefit in terms of risk reduction for death and death/MI. In addition, long-term follow-up of the FRISC-2 and RITA-3 trials confirmed that a significant improvement in outcome could be achieved with revascularization.[37,38] In this setting, the ICTUS trial failed to show a significant difference between invasive and conservative strategy.[39] However, in this study, the rate of revascularization in the two arms was very similar.

It has not been consistently shown that very early intervention in patients with NSTE-ACS leads to better outcome, with the exception of the ISAR-COOL trial.[40] As previously mentioned, early hazard may be associated with early intervention.

Accordingly, currently available evidence does not mandate a systematic approach of immediate angiography in NSTE-ACS patients stabilized with a contemporary pharmacologic approach. Likewise, a routine practice of immediate transfer of stabilized patients admitted in hospitals without on-site catheterization facilities is not mandatory, but should be organized within 72 hours.

Percutaneous Coronary Intervention (PCI)

Outcome after PCI in NSTE-ACS has been markedly improved with the use of intracoronary stenting and contemporary antithrombotic and antiplatelet therapy. The safety and efficacy of a drug-eluting stent (DES) has not been prospectively tested in this specific population, although patients with NSTE-ACS represent up to 50% of patients included in most PCI trials. In view of the potentially severe consequences of acute or subacute stent thrombosis, it is advisable to use a bare metal stent (BMS) in patients scheduled to undergo extracardiac interventions or surgery that will require interruption of clopidogrel within the first year after stent implantation. As long as the concerns about the long-term safety of DES have not been assuaged, and the situation completely clarified, the choice between use of BMS or DES should be based on an individual assessment of benefit versus potential risk.[41]

Coronary Artery Bypass Graft (CABG)

The proportion of patients with NSTE-ACS undergoing bypass surgery during the initial hospitalization is about 10%. It is important to consider the risk of bleeding complications in patients who undergo bypass surgery while initially treated with aggressive antiplatelet treatment. Overall, pretreatment with triple or even dual antiplatelet regimen should be considered as only a relative contraindication to early bypass surgery but does require specific surgical measures to minimize bleeding and platelet transfusions. (See sections on GP IIb/IIIa inhibitors and Thrombocytopenia).

Respective Indications for Percutaneous Coronary Intervention or Coronary Artery Bypass Graft

With the exception of an urgent procedure, the choice of revascularization technique in NSTE-ACS is the same as for elective revascularization procedures. From the randomized controlled trials comparing multivessel stented PCI with bypass surgery, there was no interaction between the presence of NSTE-ACS, treatment strategy, and outcome.

Recommendations for Invasive Evaluation and Revascularization

- Urgent (<120 min) coronary angiography is recommended in patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias, or hemodynamic instability (I-C).
- Early (<72 hours) coronary angiography followed by revascularization (PCI or CABG) in patients with intermediate to high-risk features is recommended (I-A).
- Routine invasive evaluation of patients without intermediate to high risk features is not recommended (III-C), but noninvasive assessment of inducible ischemia is advised (I-C).

- PCI of nonsignificant lesions by angiography is not recommended (III-C).
- After critical evaluation of the risk-to-benefit ratio, and depending on known comorbidities and potential need for noncardiac surgery in the short or medium term (e.g. planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted (BMS or DES) (I-C).

LONG-TERM MANAGEMENT

Patients with NSTE-ACS after the initial phase carry a high risk of recurrence of ischemic events. Therefore, active secondary prevention is an essential element of long-term management. Several measures and therapies have been proven to be effective in reducing the risk of recurrence of events after NSTE-ACS either in clinical randomized trials, or in observational studies and registries. However, several registries have shown that these lifestyle measures and drug therapies are underused. The role of the physician is to make sure that NSTE-ACS patients receive the appropriate therapy and lifestyle counseling in order to improve long-term outcome. It is beyond the scope of this document to review in detail all the measures and treatments that should be implemented for secondary prevention, but emphasis will be placed on those of paramount importance. Detailed recommendations on secondary prevention have been extensively described in other guidelines.[42-45]

Lifestyle interventions, weight reduction, blood pressure control, and adequate glycemic balance must be achieved in all patients for secondary prevention.

Interventions on the lipid profile, particularly low-density lipoproteins (LDL), high-density lipoproteins (HDL), and cholesterol, as well as triglycerides, are important components of long-term management.

Recent guidelines recommend combining dietary interventions with pharmacotherapy by statins to reduce LDL cholesterol to less than 100 mg/dL (<2.6 mmol/L).[42-45] Early prescription of statins during the acute phase of NSTE-ACS may have an impact on outcome. More recently, it was shown that lower LDL-cholesterol (LDL-C) targets may lead to better outcomes. In the PROVE IT study, further reduction of LDL cholesterol to a median level of 62 mg/dL (1.6 mmol/L), with aggressive lipid-lowering therapy led to a further reduction of the primary composite endpoint. Thus, intensive lipid-lowering therapy, associated with reductions in the levels of LDL cholesterol or hsCRP to values of less than 70 mg/dL (1.81 mmol/L) or less than 2 mg/L respectively, leads to improved outcome after ACS. No improvement in outcome has ever been demonstrated with any other lipid-lowering agents (e.g., fibrates, ezetimibe, nicotinic acid).

Antiplatelet agents and beta blockers have to be prescribed for the long term. Clopidogrel should be interrupted after 1 year. Angiotensin-converting enzyme (ACE) inhibitors are indicated in patients with depressed LV function or heart failure. They are also indicated in patients without these features, since meta-analysis has shown in patients without LV dysfunction or heart failure, ACE inhibitors can reduce mortality by 14% at 4 years.[46-48] Angiotensin II receptor blockers should be considered if ACE inhibitors are contraindicated or poorly tolerated. Aldosterone receptor antagonists should be considered in patients after MI who are already treated with ACE inhibitors and beta blockers, and who have a low ejection fraction, diabetes, or heart failure without significant renal dysfunction or hyperkalemia.

Rehabilitation and return to physical activity are a part of secondary prevention measures.

Recommendations for Lipid-Lowering Therapy

- Statins are recommended for all NSTE-ACS patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1-4 days) after admission, in the aim of achieving LDL-C levels of less than 100 mg/dL (<2.6 mmol/L) (I-B).
- Intensive lipid-lowering therapy with target LDL-C levels of less than 70 mg/dL (<1.81 mmol/L) initiated within 10 days after admission, is advisable (IIa-B).

Recommendations for Use of Beta Blockers

- Beta blockers should be given to all patients with reduced LV function (I-A).

Recommendations for Use of ACE Inhibitors

- ACE inhibitors are indicated long-term in all patients with LVEF of less than or equal to 40% and in patients with diabetes, hypertension or CKD, unless contraindicated (I-A).
- ACE inhibitors should be considered for all other patients to prevent recurrence of ischemic events (IIa-B). Agents and doses of proven efficacy are recommended (IIa-C).

Recommendations for Use of Angiotensin-Receptor Blockers

- Angiotensin-receptor blockers should be considered in patients who are intolerant to ACE inhibitors and/or who have heart failure or MI with LVEF of less than 40% (I-B).

Recommendations for Aldosterone Receptor Antagonists

- Aldosterone blockade should be considered in patients after MI who are already treated with ACE inhibitors and beta blockers, and who have a LVEF of less than 40% and either diabetes or heart failure, without significant renal dysfunction or hyperkalemia (I-B).

Recommendations for Rehabilitation and Return to Physical Activity

- After NSTE-ACS, assessment of functional capacity is recommended (I-C).
- Every patient after NSTE-ACS should undergo an ECG-guided exercise test (if technically feasible), or an equivalent noninvasive test for ischemia, 4 to 7 weeks after discharge (IIa-C).
- Based on cardiovascular status and on the results of functional physical capacity assessment, patients should be informed about the timing of resumption and the recommended level of physical activity, including leisure, work, and sexual activities (I-C).

COMPLICATIONS AND THEIR MANAGEMENT

Bleeding Complications

Bleeding complications have recently emerged as a major predictor of poor outcome in many clinical conditions, including NSTE-ACS. The frequency of major bleeding ranges

from 2% to 8%. Advanced age, female sex, history of bleeding, use of invasive strategy, history of renal insufficiency, and use of GP IIb/IIIa inhibitors are the most powerful predictors of bleeding. Additionally, excessive doses of drugs are often administered to women, the elderly, and patients with renal failure, increasing the risk. Renal dysfunction plays a critical role, with an exponential increase in the risk of bleeding with declining creatinine clearance.[49]

Bleeding has a strong impact on prognosis. Depending on the reports, there is a threefold to fivefold increase in the risk of death at 30 days and long-term in patients who bled during the acute phase as compared with those who did not. The same impact on prognosis has been shown, irrespective of the origin of the bleeding (procedure-related or not). Furthermore, bleeding has a deleterious impact on the risk of MI recurrence and stroke.

Many factors contribute to the worse outcome associated with bleeding. The need to discontinue antiplatelet and antithrombotic drugs certainly plays a major role. It is also important to note that the risk factors for bleeding are virtually the same as the risk factors for further ischemic events. Risk assessment in patients with NSTE-ACS needs to address the risk of both thrombotic and bleeding complications.

Prevention of bleeding encompasses the choice of safer drugs, appropriate dosage (taking into account age, gender and CrCl), reduced duration of antithrombotic treatment, use of combination of antithrombotic and antiplatelet agents according to proven indications, as well as the choice of radial over femoral approach if angiography or PCI is being considered.

Neutralization of anticoagulants and antiplatelet agents may be necessary in case of major bleeding complications. This requires specific intervention, since not all anticoagulants have an antidote, and both aspirin and clopidogrel are irreversible. In selected cases, platelet transfusion or use of cryoprecipitates, or recombinant factor VII, may be necessary, depending on the drugs used and the clinical situation.

Impact of Blood Transfusion

Blood transfusion can be required to control anemia and hemodynamic compromise. However, there is ongoing controversy about its real efficacy and safety in the context of NSTE-ACS. Blood transfusion has been shown to be associated with an increased risk of death, MI, and refractory ischemia.[50]

It is not clearly understood why transfusion may be associated with adverse outcome. Alterations in erythrocyte, nitric oxide biology in stored blood, and high hemoglobin oxygen affinity due to a low rate of 2,3-diphosphoglyceric acid, leading to decreased oxygen delivery to tissues, have been put forward, as well as increases in inflammatory mediators.

All in all, the information about the efficacy of and the indications for blood transfusion needs to be critically considered. In mild to moderate anemia (hematocrit > 25% or hemoglobin levels >8 g/dL), blood transfusion may be associated with increased risk of death at 30 days and should be avoided if anemia is hemodynamically well tolerated. Below these hematocrit/hemoglobin levels blood transfusion should be given.[50]

Recommendations for Bleeding Complications

- Assessment of bleeding risk is an important component of the decision-making process. Bleeding risk is increased with higher or excessive doses of antithrombotic agents, length of treatment, combinations of several antithrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender, baseline hemoglobin, and invasive procedures (I-B).
- Bleeding risk should be taken into account when deciding on a treatment strategy. Drugs, combinations of drugs, and nonpharmacologic procedures (vascular access) known to carry a reduced risk of bleeding should be preferred in patients at high risk of bleeding (I-B).
- Minor bleeding should preferably be managed without interruption of active treatments (I-C).
- Major bleeding requires interruption and/or neutralization of both anticoagulant and antiplatelet therapy, unless bleeding can be adequately controlled by specific hemostatic intervention (I-C).
- Blood transfusion may have deleterious effects on outcome, and should therefore be considered individually, but withheld in hemodynamically stable patients with hematocrit of more than 25% or hemoglobin level greater than 8 g/L (I-C).

Thrombocytopenia

Thrombocytopenia occurring during the treatment of NSTE-ACS is likely to be due to heparin-induced thrombocytopenia (HIT), or GP IIb/IIIa inhibitor-induced thrombocytopenia. It is impossible to distinguish between the two types, and therefore the recommendation is to interrupt both heparin and GP IIb/IIIa inhibitors. The use of anticoagulants devoid of any risk of HIT may be required if anticoagulation needs to be maintained. Severe thrombocytopenia induced by GP IIb/IIIa inhibitors requires platelet transfusion with or without fibrinogen supplementation with fresh frozen plasma or cryoprecipitate in case of bleeding.

Recommendations for Thrombocytopenia

- Significant thrombocytopenia (<100,000/μL or >50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs (I-C).
- Severe thrombocytopenia (<10,000/μL) induced by GP IIb/IIIa inhibitors requires platelet transfusion with or without fibrinogen supplementation with fresh frozen plasma or cryoprecipitate in case of bleeding (I-C).
- Interruption of heparin (UFH or LMWH) is warranted in case of documented or suspected HIT. In case of thrombotic complications, anticoagulation can be achieved with direct thrombin inhibitors (DTI) (I-C).
- Prevention of HIT can be achieved with use of anticoagulants devoid of risk of HIT, such as fondaparinux or bivalirudin, or by brief prescription of heparin (UFH or LMWH) in case these compounds are chosen as anticoagulant (I-B).

SPECIAL POPULATIONS AND CONDITIONS

Some special populations deserve additional considerations for the management of NSTE-ACS. The following groups of patients are at substantial risk of adverse cardiac events or merit alternative therapeutic strategies. Although discussed separately, there is great overlap between the subgroups, e.g., many elderly patients are women and/or have renal dysfunction, diabetes, or anemia. In this section some considerations for these populations will be provided. Comprehensive reviews can be found elsewhere.

The Elderly

There is a substantial increase of elderly patients with CAD worldwide. Although there is no common definition of what represents elderly, either age older than 65 or older than 75

years are the two most common definitions. While such dichotomous cut-offs are generally helpful, it should be recognized that the risk for mortality increases in a continuous curvilinear manner with each decade after age 50. Thus the risk of cardiac adverse events such as death, stroke, MI, and heart failure is substantial among patients over the age of 75 with CAD.[51]

The diagnosis of NSTE-ACS is often delayed due to paucity of symptoms in the elderly. The risk of death and MI increases with age. In addition, the risk of bleeding is higher in elderly patients, who often have associated comorbidities, particularly chronic renal disease. In the elderly, a strict balance between benefit and risk should be maintained.

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Recommendations for Elderly Patients

- Elderly patients (>75 years) often have atypical symptoms. Active screening for NSTE-ACS should be initiated at lower levels of suspicion than among younger (<75 years) patients (I-C).
- Treatment decisions in the elderly should be tailored according to estimated life expectancy, patient wishes, and comorbidities to minimize risk and improve morbidity and mortality outcomes in this frail but high-risk population (I-C).
- Elderly patients should be considered for routine early invasive strategy, after careful evaluation of their inherent raised risk of procedure-related complications, especially during CABG (I-B).

Gender

There is an ongoing controversy about whether or not female patients derive the same benefit as their male counterparts from currently recommended therapy for NSTE-ACS. In particular, revascularization has been questioned, as some reports failed to show any significant benefit in women with early revascularization. However, it is clear that women in general are less likely to receive evidence-based therapies, including diagnostic procedures in NSTE-ACS. As regards revascularization, a recent meta-analysis showed that it was as efficacious in women as in men.[52]

Recommendations for Women

- Women should be evaluated and treated in the same way as men, with special attention to comorbidities (I-B).

Diabetes Mellitus

The presence of diabetes mellitus is an independent predictor of higher mortality among patients with NSTE-ACS, as compared with nondiabetic patients. Diabetic patients have more comorbid illnesses, including impaired renal function, heart failure, stroke, and general vascular disease. Diabetics are often undertreated compared with nondiabetics, whereas they derive the same magnitude of benefit from therapy as patients without diabetes.[53]

Good glycemic control with standard pharmacologic approaches, and revascularization, including use of GP IIb/IIIa inhibitors are recommended in diabetic patients.

A comprehensive approach to primary and secondary prevention is also strongly recommended, focusing particularly on lipid levels, blood pressure, and glycemic control.

Recommendations for Diabetes

- Tight glycemic control to achieve normoglycemia as soon as possible is recommended in all diabetic patients with NSTE-ACS in the acute phase (I-C).
- Insulin infusion may be needed to achieve normoglycemia in selected NSTE-ACS patients with high blood glucose levels at admission (IIa-C).
- Early invasive strategy is recommended for diabetic patients with NSTE-ACS (I–A).
- Diabetic patients with NSTE-ACS should receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management, which should be continued through the completion of PCI (IIa–B).

Chronic Kidney Disease (CKD)

Renal dysfunction is frequently observed in NSTE-ACS as in other forms of CAD.[54] In OASIS-5, 49.3% of patients had CrCl of less than 71 mL/min (upper limit of the second quartile of CrCl), which represents moderate renal dysfunction, and 2.6% had CrCl of less than 30 mL/min. Renal dysfunction is associated with worse prognosis in patients with overt clinical manifestations of atherosclerosis, including NSTE-ACS, STE-ACS, and PCI, as well as in diabetic patients. In addition, renal dysfunction is a potent independent predictor of bleeding risk in patients with ACS; the more severe being the dysfunction, the higher the bleeding risk.

The presence of renal dysfunction complicates the management of patients suffering from NSTE-ACS, because many of the drugs, especially anticoagulants, are either partially or totally eliminated by the renal route. Overdosage and its associated inherent risk of bleeding is common in patients with renal failure. Furthermore, the risk of contrast-induced nephropathy should encourage clinicians to actively prevent further deterioration of renal function, paying special attention to hydration, use of limited quantities of contrast medium, and low or iso-osmolar contrast medium at the time of angiography and angioplasty.

Like diabetics, patients with CKD are often undertreated, and in particular are submitted less often to revascularization, whereas they are at much higher risk than patients without renal failure.

Recommendations for Patients With Chronic Kidney Disease

- CrCl and/or GFR should be calculated for every patient hospitalized for NSTE-ACS (I-B). Elderly people, women, and low–body-weight patients merit special attention as near-normal serum creatinine levels may be associated with lower than expected CrCl and GFR levels (I-B).
- Patients with CKD should receive the same first-line treatment as any other patient, in the absence of contraindications (I-B).
- Anticoagulants should be carefully dosed. In patients with CrCl less than 30 mL/min or GFR less than 30 mL/min/1.73 m^2, bivalirudin should be used at reduced doses, whereas fondaparinux, enoxaparin, and other LMWHs are contraindicated (I-B).
- UFH infusion adjusted according to aPTT is recommended when CrCl is less than 30 mL/min or GFR is less than 30 mL/min/1.73 m^2 (I-C).
- GP IIb/IIIa inhibitors can be used in case of renal failure. Dose adaptation is needed with eptifibatide and tirofiban. Careful evaluation of the bleeding risk is recommended for abciximab (I-B).
- Patients with CKD with CrCl of less than 60 mL/min are at high risk of further ischemic events and therefore should be submitted to invasive evaluation and revascularization whenever possible (IIa-B).
- Appropriate measures are advised to reduce the risk of contrast-induced nephropathy (I-B).

Anemia

Anemia has been shown to be associated with worse prognosis, and particularly higher mortality in various conditions, including heart failure, renal failure, various types of surgery and malignancy, but also across the whole spectrum of CAD, including STEMI, NSTE-ACS, PCI, and CABG.[55]

Baseline hemoglobin was also shown to be an independent predictor of the risk of bleeding; the lower the baseline hemoglobin, the higher the risk, for both procedure-related and non–procedure-related bleeding. Therefore, as modern treatment of NSTE-ACS may lead to a worsening of anemia, because of increased risk of bleeding, special attention has to be paid to baseline hemoglobin level when deciding upon the therapeutic approach.

Recommendations for Anemia

- Low baseline hemoglobin is an independent marker of the risk of ischemic and bleeding events at 30 days. It should be taken into consideration in assessing initial risk (I-B).
- All necessary measures should be taken during the course of initial management to avoid worsening of anemia by bleeding (I-B) (see section on Bleeding complications).
- Well tolerated anemia at baseline in patients with NSTE-ACS should not lead to systematic blood transfusion, which should be considered only in case of compromised hemodynamic status (I-C) (see section on Bleeding Complications).

Normal Coronary Arteries

A sizeable proportion of patients with NSTE-ACS have normal coronary arteries or only minor abnormalities. The pathophysiology of NSTE-ACS is not homogeneous and possible mechanisms include: (1) a coronary artery spasm (Prinzmetal's angina); (2) an intramural plaque complicated by acute thrombosis with subsequent recanalization; (3) coronary emboli; (4) syndrome X; and (5) apical ballooning.[56]

MANAGEMENT STRATEGY

NSTE-ACS encompasses a heterogeneous spectrum of patients with different levels of risk in terms of death, MI, or recurrence of MI. In the following paragraphs, a stepwise strategy is outlined that is based on the above detailed analysis of the available scientific data and which should be applicable to most patients admitted with suspected NSTE-ACS. It must be appreciated, however, that specific findings in individual patients may result in appropriate deviations from the proposed strategy. For every patient, the physician must make an individual decision, taking into account the patient's history (comorbid illnesses, age, etc.), his or her clinical condition, findings during the initial assessment on first contact, and the available pharmacologic and nonpharmacologic treatment options.

First Step: Initial Evaluation

Chest pain or discomfort will be the symptom that leads the patient to seek medical attention or hospitalization. A patient with suspected NSTE-ACS must be evaluated in a hospital and immediately seen by a qualified physician. Specialized chest pain units provide the best and expeditious care.

The initial step is to assign the patient without delay to a working diagnosis on which the treatment strategy will be based. The criteria are:

- Quality of chest pain and a symptom-oriented physical examination
- Assessment of the likelihood of CAD (e.g., age, risk factors, previous MI, CABG, PCI)
- ECG (ST deviation or other ECG abnormalities)

Based on these findings, which should be available within 10 minutes after first medical contact, the patient can be assigned to one of the three major working diagnoses:

- STEMI requiring immediate reperfusion
- NSTE-ACS
- ACS (highly) unlikely

The treatment of patients with STEMI is covered in the respective guidelines. The assignment to the category "unlikely" must be done with caution and only when another explanation is obvious (e.g., trauma). Additional ECG leads (V_3R and V_4R, V_7-V_9) should be recorded, especially in patients with persisting chest pain.

Blood is drawn on arrival of the patient in hospital and the result should be available within 60 minutes to be used in the second strategy step. Initial blood tests must at least include: troponin T or troponin I, creatine kinase (-MB), creatinine, hemoglobin, and leukocyte count.

The assignment to the category NSTE-ACS will result in the second strategy step.

Second Step: Diagnosis Validation and Risk Assessment

Diagnosis Validation

After the patient is assigned to the NSTE-ACS group, intravenous and oral treatments will be started.

The first-line treatment should include at least nitrates, beta blockers, aspirin, clopidogrel and anticoagulation, the type of which depends on the management strategy: urgent invasive, early invasive, or conservative (see third step).

Typically, anticoagulation should be administered in the form of fondaparinux for all patients except those requiring urgent invasive strategy (<2 hours following admission), since in these patients, UFH will be required in case of PCI. In all other patients, anticoagulation with fondaparinux can be initiated.

All patients should receive aspirin and clopidogrel.

GP IIb/IIIa inhibitors are indicated in patients with urgent or early invasive strategy, but not in conservative strategy.

The further management will be based on additional information and data:

- Routine clinical chemistry, particularly troponins (on presentation and after 6 to 12 hours) and other markers according to working diagnoses (e.g. D-dimers, BNP, NT-proBNP)
- Repeat, preferably continuous, ST-segment monitoring (when available)
- Echocardiogram, MRI, CT, or nuclear imaging for differential diagnoses (e.g., aortic dissection, pulmonary embolism)
- Responsiveness to antianginal treatment
- Risk score assessment
- Bleeding risk assessment

During this step other diagnoses may be confirmed or excluded, including acute anemia, pulmonary embolism, aortic aneurysm (see section on Differential Diagnosis).

Risk Assessment

The treatment of the individual patient is tailored according to the risk for subsequent events, which should be assessed early at the initial presentation as well as repeatedly thereafter in the light of continuing or repetitive symptoms and additional information from clinical chemistry or imaging modalities.

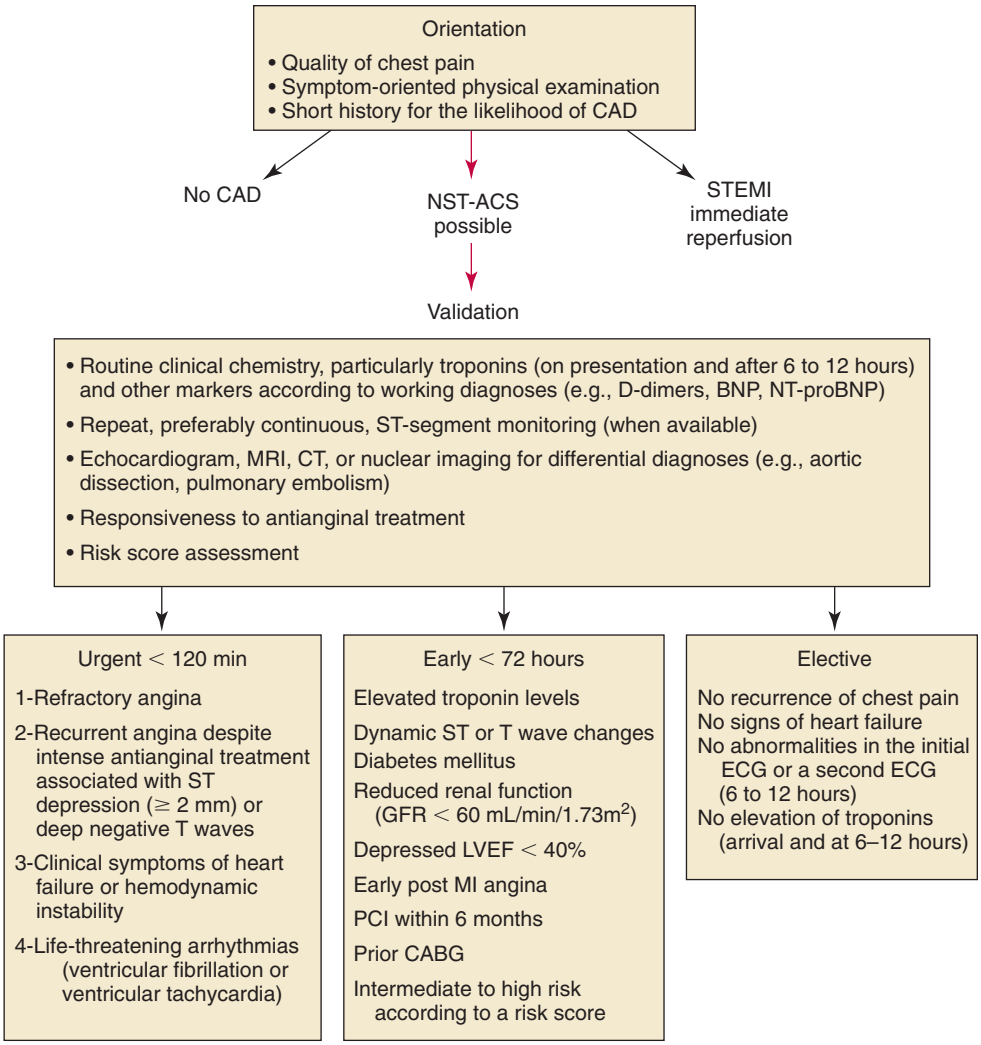

FIGURE 33–1 Decision-making algorithm for the management of non–ST-segment elevation acute coronary syndromes.

Risk assessment is an important component of the decision-making process and is subject to constant re-evaluation. It encompasses assessment of both ischemic and bleeding risk. The risk factors for bleeding and ischemic events overlap considerably, with the result that patients at high risk of ischemic events are also at high risk of bleeding complications. Therefore, the choice of the pharmacologic environment (dual or triple antiplatelet therapy, anticoagulants) has become critical, as has the dosage of the drugs. Additionally, in case invasive strategy is needed, the choice of the vascular approach is very important, since the radial approach has been shown to reduce the risk of bleeding as compared with the femoral approach. In this context, particular attention has to be paid to renal dysfunction, shown to be particularly frequent in elderly patients and among diabetics.

During this step, the decision has to be made whether the patient should go on to cardiac catheterization or not.

Third Step: Invasive Strategy

Cardiac catheterization is advised to prevent early complications and/or to improve long-term outcome (Fig. 33-1). Accordingly, the need for and timing of invasive strategy has to be tailored according to the acuteness of risk into three categories: conservative, urgent invasive, or early invasive.

Conservative Strategy

Patients who fulfill all below criteria may be regarded as low risk and should not be submitted to early invasive evaluation. Pharmacologic approach includes aspirin, clopidogrel, fondaparinux, and beta blockers. These patients have the following characteristics:

- No recurrence of chest pain
- No signs of heart failure
- No abnormalities in the initial ECG or a second ECG (6 to 12 hours)
- No elevation of troponins (arrival and at 6 to 12 hours)

Low risk as assessed by a risk score (see section on Risk Stratification) can support the decision-making process for a conservative strategy. The further management in these patients is according to the evaluation of stable CAD. Before discharge, a stress test for inducible ischemia is useful for further decision making.

Patients who cannot be excluded by the above criteria should go on to cardiac catheterization.

Urgent Invasive Strategy

Urgent invasive strategy (<120 min) should be undertaken for patients who are early in the process of developing major myocardial necrosis escaping the ECG (e.g., occlusion of the circumflex artery) or are estimated to be at high risk of rapid

progression to vessel occlusion. These patients are characterized by:

- Refractory angina (e.g., evolving MI without ST abnormalities)
- Recurrent angina despite intense antianginal treatment associated with ST depression (≥2 mm) or deep negative T waves
- Clinical symptoms of heart failure or hemodynamic instability ("shock")
- Life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia)

Typically, these patients should receive aspirin, clopidogrel, and a GP IIb/IIIa inhibitor (tirofiban, eptifibatide). Fondaparinux is not recommended as an anticoagulant in this situation, because these patients will require UFH in the catheterization laboratory if PCI is to be carried out. These patients must be taken to the catheterization laboratory within 2 hours.

Early Invasive Strategy

Some patients initially respond to the antianginal treatment, but are at increased risk and need early angiography. The timing depends on the local circumstances, but it should be performed within 72 hours.

The following features indicate patients who should undergo routine early angiography:

- Elevated troponin levels
- Dynamic ST or T wave changes (symptomatic or silent) (≥0.5mm)
- Diabetes mellitus
- Reduced renal function (GFR <60 mL/min/1.73 m^2)
- Depressed LVEF less than 40%
- Early post MI angina
- PCI within 6 months
- Prior CABG
- Intermediate to high risk according to a risk score

These patients should receive aspirin, clopidogrel, fondaparinux, and a GP IIb/IIIa inhibitor (tirofiban, eptifibatide) prior to catheterization in case of elevated troponins, dynamic ST/T changes, or diabetes provided there is no overt excessive bleeding risk.

The decision about the timing of catheterization must continuously be re-evaluated and modified according to clinical evolution and occurrence of new clinical findings.

Fourth Step: Revascularization Modalities

If the angiogram shows no critical coronary lesions, patients will be referred for medical therapy. The diagnosis of NSTE-ACS may be reconsidered and particular attention should be given to other possible reasons for symptoms at presentation before the patient is discharged. However, the absence of critical coronary lesions does not rule out the diagnosis if clinical presentation was suggestive of ischemic chest pain and if biomarkers were positive. In this situation, patients should receive treatment according to recommendations in NSTE-ACS.

Recommendations for the choice of a revascularization modality in NSTE-ACS are similar to those for elective revascularization procedures. In patients with single-vessel disease, PCI with stenting of the culprit lesion is the first choice. In patients with multivessel disease the decision for PCI or CABG must be made individually. A sequential approach with treating the culprit lesion by PCI followed by elective CABG may in some patients be advantageous.

The anticoagulant should not be changed for PCI. In patients pretreated with fondaparinux, UFH must be added before PCI. In patients pretreated with tirofiban or eptifibatide, the infusion should be maintained throughout the intervention. Patients untreated with GP IIb/IIIa inhibitors should preferably receive abciximab before PCI. There is less evidence for the use of eptifibatide or tirofiban in this setting.

If CABG is planned, clopidogrel should be stopped and surgery deferred for 5 days, if the clinical condition and the angiographic findings permit this.

If angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run-off, freedom from angina at rest should be achieved by intensified medical therapy and secondary preventive measures should be instituted.

Fifth Step: Discharge and Postdischarge Management

Although in NSTE-ACS most adverse events occur in the early phase, the risk for MI or death remains elevated over several months. Patients treated with early revascularization are at low (~2.5%) risk for developing life-threatening arrhythmias, with 80% occurring during the first 12 hours after onset of symptoms. Accordingly, monitoring of the patients beyond 24 to 48 hours is not warranted.

Discharge from hospital depends on clinical and angiographic findings. Patients with NSTE-ACS should be hospitalized for at least 24 hours after successful stenting of the culprit lesion.

Intense risk factor modification is warranted in all patients following the diagnosis of NSTE-ACS.

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CHAPTER 34

ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction—A Summary Article

Jeffrey L. Anderson

Coronary artery disease (CAD) is the leading cause of death in the United States. Unstable angina (UA) and the closely related condition of non–ST-segment elevation myocardial infarction (NSTEMI) are common manifestations of this disease. Knowledge of disease pathophysiology, diagnostic approaches, management strategies, and preventive measures continue to evolve. Accordingly, the American College of Cardiology (ACC) and the American Heart Association (AHA) organized a committee to revise and update (2007) the previous guidelines published in 2000 and updated in 2002.

OVERVIEW OF CHANGES

The writing committee considered evidence published since 2002 and drafted revised recommendations to incorporate results from major clinical trials.[1,2] In the 2007 revision, greater emphasis is placed on earlier access to medical evaluation. New imaging modalities (coronary computed tomographic angiography [CTA] and cardiac magnetic resonance imaging) are recognized as diagnostic options in selected patients.[3] Troponins are highlighted as the dominant cardiac biomarker of necrosis. B-type natriuretic peptide (BNP) has been added to the list of biomarkers potentially useful in risk assessment.[4] Supplemental posterior electrocardiograph (ECG) leads V_7 to V_9 are noted to be a reasonable diagnostic tool to assess the possibility of ST-segment elevation myocardial infarction (STEMI) caused by left circumflex occlusion.[5]

Clinical trials data are noted overall to continue to support an initial invasive strategy for higher-risk and clinically unstable UA/NSTEMI patients[6]; nevertheless, other data (ICTUS) also were reviewed that allowed an initial conservative strategy to be considered in initially stabilized patients,[7] and an initial conservative strategy is now specifically recognized as the preferred strategy in those at low risk of acute coronary syndromes (ACS), particularly low-risk women, as supported by a growing body of evidence.[8-10]

The recommendation for beta blockade is now counterbalanced with a statement on the potential for harm, especially with acute intravenous administration in those at risk of heart failure or cardiogenic shock (COMMIT).[11] Nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin should be avoided in UA/NSTEMI patients because of the recent recognition of potential harm.[12,13]

Two new anticoagulants, fondaparinux[14] and bivalirudin,[15] have undergone testing and are recommended as alternatives to unfractionated heparin (UFH) and low–molecular-weight heparins (LMWHs) for specific applications in UA/NSTEMI. Support for thienopyridine use (primarily with clopidogrel in 2007) continues to grow, including higher loading-dose options,[16] earlier (upstream) administration, and longer administration (especially after drug-eluting stent [DES] placement).[17] Evidence still supports glycoprotein (GP) IIb/IIIa receptor antagonists as providing incremental benefit in higher risk patients.[18] Special emphasis is placed on dosing adjustment (e.g., for anticoagulants and antiplatelet agents) based on creatinine clearance, especially in the elderly, in women, and in others with baseline renal insufficiency, to prevent dosing errors leading to increased bleeding risk.[19] The guidelines also incorporate recent updates for secondary and primary prevention.[20] An expanded section recognizes special diagnostic and therapeutic considerations in special patient groups, and care processes are highlighted as an area important to short- and long-term patient outcomes.

Nearly simultaneously, the European Society of Cardiology (ESC) also published guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes.[21] These complementary guidelines are recommended for additional reading and insights into the evaluation and management of this condition.

Classification of Recommendations

The schema for classification and level of evidence of recommendations follow that of the previous version of these and other recent ACC/AHA guidelines. These can be summarized briefly as follows:

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective (i.e., the procedure/treatment SHOULD be performed/administered).
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy (i.e., IT IS REASONABLE to perform procedure/administer treatment).
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion (i.e., the procedure/treatment MAY BE CONSIDERED).
- Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful (i.e., the procedure/treatment should NOT be performed/administered).

The weight of evidence is ranked separately from the class recommendation as (A), highest, if data were derived from multiple randomized clinical trials or meta-analyses that involved sufficiently large numbers of patients and multiple population risk strata, and (B), intermediate, if data were derived from a single randomized trial or nonrandomized studies with limited population risk strata evaluated. The lowest rank (C) was given when expert opinion, case studies, or standard-of-care formed the primary basis for the recommendation.

OVERVIEW OF ACUTE CORONARY SYNDROMES

Acute coronary syndromes (ACS) represent a major health problem. The National Center for Health Statistics report for 2007 indicates that 1,565,000 hospitalizations occurred in 2004 for a primary or secondary diagnosis of an acute coronary syndrome: 669,000 for UA and 896,000 for myocardial infarction (MI).[22] In the spectrum of ACS, UA/NSTEMI is defined by ECG ST-segment depression or prominent T wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (i.e., chest discomfort or anginal equivalent). The importance of this syndrome is emphasized by the fact that approximately three-quarters (1.24 million) of ACS hospitalizations annually are for UA/NSTEMI and the other quarter (0.33 million) for ST-segment elevation MI (STEMI).[22] UA/NSTEMI is usually, but not always, a complication of atherothrombotic coronary artery disease (CAD) leading to a marked reduction in oxygen supply to the myocardium and an increased risk of subsequent MI and cardiac death.

Initial Evaluation and Management

Delays in recognition of the symptoms of UA/NSTEMI and presentation to the medical care system remain a challenge for optimal medical care. There is a continued need to stress earlier recognition and presentation for care, which can reduce morbidity and mortality. Currently, the average delay after symptom onset is approximately 2 hours.[23] Reasons for delay include a mismatch between expectation and actual symptoms, an impression that symptoms are self-limited, or attribution of symptoms to other conditions. Also, ACS/MI may be clinically silent, unrecognized, or associated with symptoms other than chest discomfort (such as dyspnea) in one third to one half of cases.[24,25] Older patients, women, and diabetics are more likely to have a silent or atypical presentation.

When first contacted, health care providers should advise patients with possible ACS that evaluation cannot be performed solely via the telephone, and they should especially target those with known coronary heart disease (CHD) or equivalents. Instructions to administer aspirin may be given. When symptoms are moderate to severe or sustained (e.g., >20 min), unresponsive to 1 nitroglycerin (NTG) dose (if available and administered), and MI is suspected, patients should be instructed to access the emergency medical system (EMS) by dialing 911 and be transported to hospital by ambulance. On arrival, these patients should be considered high priority and evaluated by a predetermined algorithm (Fig. 34-1) aimed at addressing two specific questions: what is the likelihood that symptoms represent ACS, and what is the likelihood of an adverse clinical outcome?

Early Risk Stratification

An estimation of risk is useful in selection of the level of initial medical care and initial medical and interventional therapies. This risk is assessed by integrating features of the initial medical history, physical examination, ECG (goal, within 10 min of emergency department [ED] arrival), renal function, and cardiac biomarker measurements. The application of quantitative risk scores developed in recent years (e.g., TIMI, GRACE, and PURSUIT risk scores) is expected to assist with short- as well as longer-term risk assessment (Table 34-1).[26] Overall, risk is highest at presentation then declines but remains elevated above baseline for at least 1 to 3 months beyond the acute stage.

It should be recognized that three fourths of patients evaluated in the ED for suspected ACS will be found not to have acute ischemia and require further evaluation, triage, and treatment as indicated by their underlying symptoms and condition.[27]

Cardiac Biomarkers of Necrosis. The sensitivity and specificity of the cardiac troponins I and T have made them the diagnostic biomarkers of choice and inspired the redefinition of acute myocardial infarction (AMI).[28] Further, they may identify high-risk patients who will benefit from aggressive medical and interventional therapies. Myocardial necrosis now is defined as an elevation of troponin above the 99th percentile of normal, and MI is defined as necrosis related to ischemia. The diagnosis of AMI must be based on troponin elevation supplemented with other clinical and laboratory features,[28] because detectable elevations of troponin are commonly observed with other conditions using the newer, highly sensitive troponin assays.

Troponins can be detected in blood as early as 2 to 4 hours after symptom onset, but elevation can be delayed for up to 8 to 12 hours. The timing of initial elevation is similar to that of creatine kinase (CK)-MB but persists longer, that is, for 5 to 14 days (Fig. 34-2). CK-MB remains useful for the diagnosis of early infarct extension (reinfarction) and for periprocedural MI because its short half-life is well suited to detecting secondary marker increases. A newer method aims to identify MI earlier by relying on *changes* in serum marker levels (delta values) over an abbreviated time interval (e.g., 2 hours) when markers may be still in the normal or indeterminate range.[29]

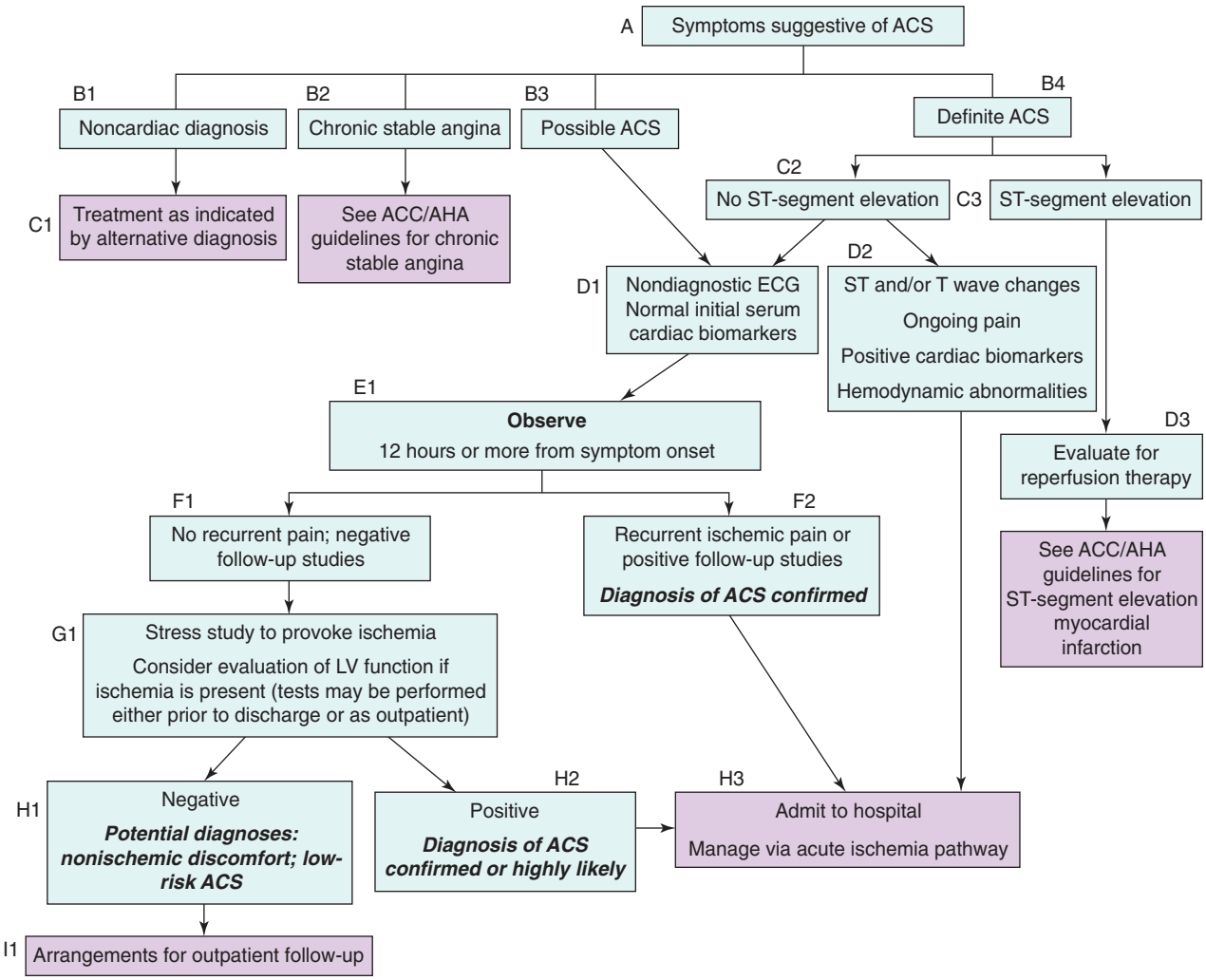


FIGURE 34–1 Algorithm for evaluation and management of patients with suspected ACS. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

TABLE 34–1 TIMI Risk Score for Unstable Angina/Non–ST Elevation Myocardial Infarction

TIMI Risk Score	All-Cause Mortality, New or Recurrent Myocardial Infarction, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days after Randomization
0-1	4.7%
2	8.3%
3	13.2%
4	19.9%
5	26.2%
6-7	40.9%

The TIMI risk score is determined by the sum of the presence of seven variables present at admission; one point is given for each of the following variables:
- Age 65 years or older
- At least 3 risk factors for CAD
- Prior coronary stenosis of 50% or more*
- ST segment deviation on ECG presentation
- At least 2 anginal events in prior 24 hours
- Use of aspirin in prior 7 days
- Elevated serum cardiac biomarkers

*Variable remained relatively insensitive to missing information and remained a significant predictor of events. The TIMI risk tool can be accessed at www.timi.org.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.

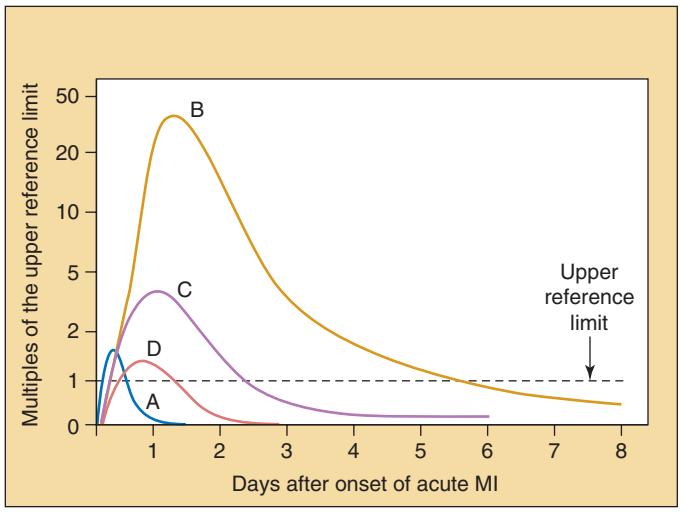


FIGURE 34–2 Kinetics of biomarkers following acute myocardial infarction. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

Other Biomarkers. Biomarkers of other pathophysiologic mechanisms implicated in ACS and multimarker approaches are currently under investigation. B-type natriuretic peptides have been shown to provide incremental prognostic value in patient cohorts with STEMI and UA/NSTEMI and now may be used to supplement risk assessment.[4]

Initial Triage and Immediate Management. Based on initial clinical risk assessment, patients can be assigned and managed according to one of four categories: noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS, which is further divided into UA/NSTEMI and STEMI, based on the initial ECG (see Fig. 34-1). Emergency department–based chest pain evaluation units have been found to be helpful to avoid both unnecessary hospital admissions as well as inappropriate ED discharges.[30] Patients at low ACS risk (see Fig. 34-1, box F1) may be considered for a predischarge stress test or coronary CT angiogram. Alternatively, they may be discharged with appropriate medications and instructions and return for testing within 72 hours. Patients with definite or probable ACS, including those with ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T wave inversions, hemodynamic abnormalities, or a positive stress test are admitted to the hospital for further management.

Selected Recommendations for Initial Evaluation and Management

A. Clinical Assessment

Class I

1. Patients with definite symptoms of ACS (chest discomfort with or without radiation to the arm[s], back, neck, jaw, or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be instructed to call 911 and should be transported to the hospital by ambulance rather than by friends or relatives. (*Level of Evidence* [*LOE*]*: B*)
2. Prehospital EMS providers should administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having ACS unless contraindicated or already taken by the patient. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations. (*LOE: C*)
3. Health care providers should instruct patients with suspected ACS for whom NTG has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort or pain. If chest discomfort or pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member, friend, or caregiver call 911 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member, friend, or caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 911 if symptoms have not resolved completely. (*LOE: C*)
4. Patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for greater than 20 minutes, hemodynamic instability, or recent syncope or presyncope should be referred immediately to an ED. Other patients with a suspected ACS who are experiencing less severe symptoms and who have none of the above high-risk features, including those who respond to an NTG dose, may be seen initially in an ED or an outpatient facility able to provide an acute evaluation. (*LOE: C*)

B. Early Risk Stratification

Class I

1. A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management. (*LOE: C*)
2. A 12-lead ECG should be performed and shown to an experienced emergency physician as soon as possible after ED arrival, with a goal of within 10 minutes of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of ACS. (*LOE: B*)
3. A cardiac-specific troponin is the preferred biomarker, and, if available, should be measured in all patients who present with chest discomfort consistent with ACS. CK-MB by mass assay is acceptable but not preferred. (*LOE: B*)
4. Patients with negative cardiac biomarkers within 6 hours of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 hours after symptom onset. (*LOE: B*)

Class IIa

1. Use of risk-stratification models, such as the Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk score or the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model, can be useful to assist in decision making regarding treatment options in patients with suspected ACS. (*LOE: B*)
2. It is reasonable to obtain supplemental ECG leads V_7 through V_9 in patients whose initial ECG is nondiagnostic to rule out MI due to left circumflex occlusion. (*LOE: B*)

Class IIb

1. For patients who present within 6 hours of symptoms suggestive of ACS, a 2-hour delta CK-MB mass in conjunction with 2-hour delta troponin may be considered. (*LOE: B*)
2. Measurement of BNP or NT terminal (NT)-proBNP may be considered to supplement assessment of global risk in patients with suspected ACS. (*LOE: B*)

C. Immediate Management

Class I

1. The history, physical examination, 12-lead ECG, and initial cardiac biomarker tests should be integrated to assign patients with chest pain into one of four categories: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS. (*LOE: C*)
2. In patients with suspected ACS in whom ischemic heart disease is present or suspected, if the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, a stress test (exercise or pharmacologic) to provoke ischemia or a noninvasive coronary imaging test should be performed in the ED, in a chest pain unit, or on an outpatient basis in a timely fashion (within 72 h) as an alternative to inpatient admission. Low-risk patients with a negative diagnostic test can be managed as outpatients. (*LOE: C*)
3. Patients with definite ACS and ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T wave inversions, hemodynamic abnormalities, or a positive stress test should be admitted to the hospital for further management. Admission to the critical care unit is recommended for those with active, ongoing ischemia or injury, hemodynamic or electrical instability. Otherwise, a telemetry step-down unit is reasonable. (*LOE: C*)

Class IIa

1. In patients with suspected ACS with a low or intermediate probability of CAD, in whom the follow-up 12-lead ECG and cardiac biomarker measurements are normal, performance of a noninvasive coronary imaging test (i.e., coronary CT angiography) is reasonable as an alternative to stress testing. (*LOE: B*)

EARLY HOSPITAL CARE

GENERAL AND ANTI-ISCHEMIC THERAPY

Patients with definite or probable UA/NSTEMI are admitted for inpatient care. High-risk patients, including those with continuing discomfort, hemodynamic instability, or both should be hospitalized initially in a coronary care unit. After admission, standard medical therapy is indicated to relieve ischemia and prevent serious adverse outcomes. Unless contraindicated, general treatment for UA/STEMI patients should include aspirin, a beta blocker (preferably orally, in titrated doses), anticoagulant therapy, a GP IIb/IIIa receptor antagonist, and a thienopyridine (initiation may be deferred until a revascularization decision is made). Nitroglycerin (NTG) is indicated for treatment of persistent ischemia, heart failure, or hypertension. Supplemental oxygen is given to relieve or prevent desaturation. A critical early decision, which influences the choice of antithrombotic and other therapies, is the choice of an angiographic (invasive) or an initial conservative strategy.

Selected Recommendations: Anti-Ischemic and Analgesic Therapy

Class I

1. Bed or chair rest with continuous ECG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase. (*LOE: C*)
2. Supplemental oxygen should be administered to patients with UA/NSTEMI with an arterial saturation less than 90%, respiratory distress, or other high-risk features for hypoxemia. Pulse oximetry is useful for continuous measurement of SaO_2. (*LOE: B*)
3. Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. (*LOE: C*)
4. Intravenous NTG is indicated in the first 48 hours after UA/NSTEMI for treatment of persistent ischemia, heart failure (HF), or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors. (*LOE: B*)
5. Oral beta-blocker therapy should be initiated within the first 24 hours for patients without contraindications who do not have one or more of the following: (1) signs of HF; (2) evidence of a low-output state; (3) increased risk* for cardiogenic shock; or (4) relative contraindication to beta blockade (PR interval greater than or equal to 0.24 second, second- or third-degree heart block, active asthma, or reactive airway disease). (*LOE: B*)
6. In UA/NSTEMI patients with continuing or frequently recurring ischemia and in whom beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular (LV) dysfunction or other contraindications. (*LOE: B*)
7. An ACE inhibitor should be administered orally within the first 24 hours to UA/NSTEMI patients with pulmonary congestion or LV ejection fraction (LVEF) less than or equal to 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. (*LOE: A*)
8. An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiologic signs of HF or LVEF less than or equal to 0.40. (*LOE: A*)
9. Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, NSAIDS, except for aspirin, whether nonselective or cyclooxygenase (COX)-2-selective agents, should be discontinued at the time a patient presents with UA/NSTEMI. (*LOE: C*)

Class IIa

1. It is reasonable to administer supplemental oxygen to all patients with UA/NSTEMI during the first 6 hours after presentation. (*LOE: C*)
2. In the absence of contradictions to its use, it is reasonable to administer morphine sulfate intravenously to UA/NSTEMI patients if there is uncontrolled ischemic chest discomfort despite NTG, provided that additional therapy is used to manage the underlying ischemia. (*LOE: B*)
3. It is reasonable to administer intravenous beta blockers at the time of presentation for hypertension to UA/NSTEMI patients who do not have one or more of the following: (1) signs of HF; (2) evidence of a low-output state; (3) increased risk* for cardiogenic shock; or (4) relative contraindication to beta blockade (PR interval greater than or equal to 0.24 second, second- or third-degree heart block, active asthma, or reactive airway disease). (*LOE: B*)
4. Oral long-acting nondihydropyridine calcium channel blockers are reasonable for use in UA/NSTEMI patients for recurrent ischemia in the absence of contraindications after beta blockers and nitrates have been fully used. (*LOE: C*)
5. An ACE inhibitor administered orally within the first 24 hours of UA/NSTEMI can be useful in patients without pulmonary congestion or LVEF less than or equal to 0.40 in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. (*LOE: B*)
6. Intra-aortic balloon pump counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI. (*LOE: C*)

Class III

1. Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 beats/min), tachycardia (more than 100 beats/min) in the absence of symptomatic HF, or right ventricular infarction. (*LOE: C*)

*Age greater than 70 years, systolic blood pressure less than 120 mm Hg, heart rate greater than 110 or less than 60, increased time since onset of symptoms of UA/STEMI.

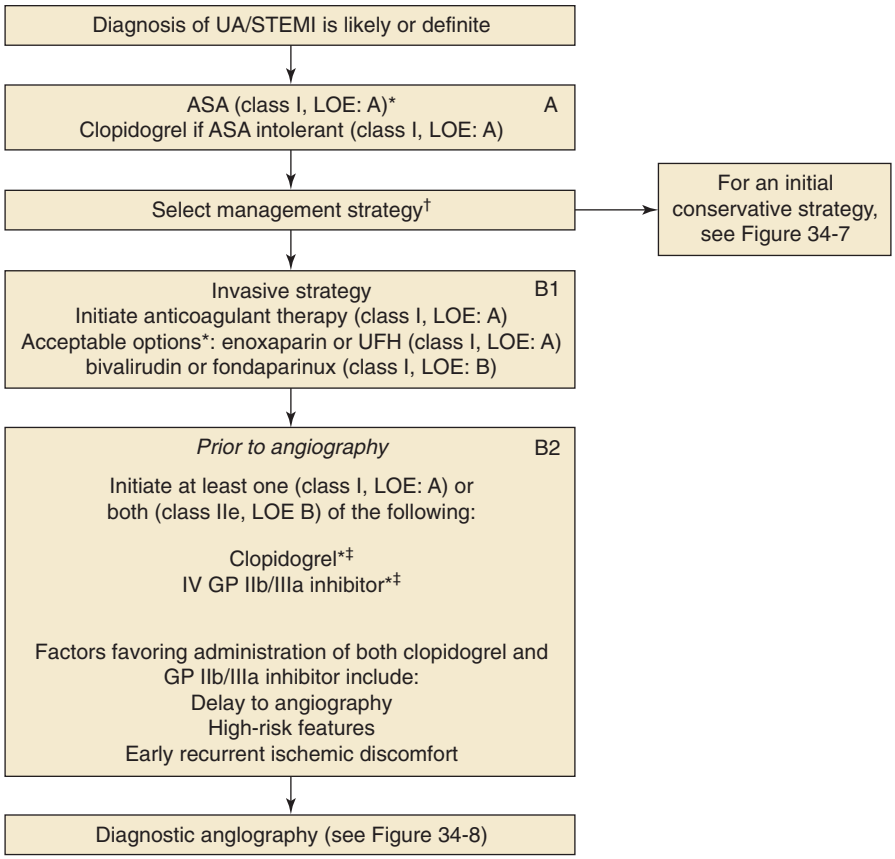


FIGURE 34–3 Algorithm for patients with UA/NSTEMI managed by an initial (early) invasive strategy. ASA, aspirin, GP, glycoprotein, LOE, level of evidence, UFH, unfractionated heparin. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

2. Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 hours of sildenafil or 48 hours of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. (*LOE: C*)
3. Immediate-release dihydropyridine calcium channel blockers should not be administered to patients with UA/NSTEMI in the absence of a beta blocker. (*LOE: A*)
4. It may be harmful to administer intravenous beta blockers to UA/NSTEMI patients who have contraindications to beta blockade, signs of HF or low-output state, or other risk factors* for cardiogenic shock (*LOE: A*)
5. Nonsteroidal antiinflammatory drugs (except for aspirin), whether nonselective or COX-2-selective agents, should not be administered during hospitalization for UA/NSTEMI because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use. (*LOE: C*)

CHOICE OF STRATEGY: INITIAL CONSERVATIVE VERSUS EARLY INVASIVE

Two general pathways have emerged for treating UA/NSTEMI patients: the early invasive strategy (Fig. 34-3) and the initial conservative strategy (Fig. 34-4).

*Age greater than 70 years, systolic blood pressure less than 120 mm Hg, heart rate greater than 110 or less than 60, increased time since onset of symptoms of UA/STEMI.

The initial conservative strategy calls for invasive evaluation only with symptomatic failure of medical therapy or other objective evidence of recurrent or latent ischemia (i.e., "selective invasive" management).[31] For stabilized patients, noninvasive stress testing (treadmill, echo, or nuclear) or coronary imaging (multislice coronary CTA) before or shortly after discharge then is used for estimating residual risk as low, intermediate, or high, and to determine the need for angiography (see Fig. 34-4). In the absence of conclusive comparative data, test selection may be based primarily on patient characteristics, physician judgment, and local availability and expertise.

In contrast, the invasive strategy calls for routine angiography, generally early during hospitalization. The initial invasive strategy can be subdivided into two groups: patients who fail to stabilize on presentation with initial medical therapy and require urgent angiography/revascularization because of ongoing ischemic/hemodynamic/rhythm instability, and a second, larger group of patients who initially stabilize but are believed to benefit from "early" (generally, within 4 to 24 hours) but nonurgent angiography/intervention. For this second invasive group, two alternatives have been studied: earlier, or more delayed, angiography (i.e., within, or after, a 12- to 48-hour window from admission). To address this, the ISAR-COOL trial randomized 410 patients to very early angiography (median time 2.4 hours) or delayed angiography (median 86 hours) during "cooling off" with intensive medical therapy. Earlier angiography resulted in fewer deaths or MIs at 30 days (5.9% vs. 11.6%; $P = .04$).[32] Additional data assessing the timing of angiography are needed.

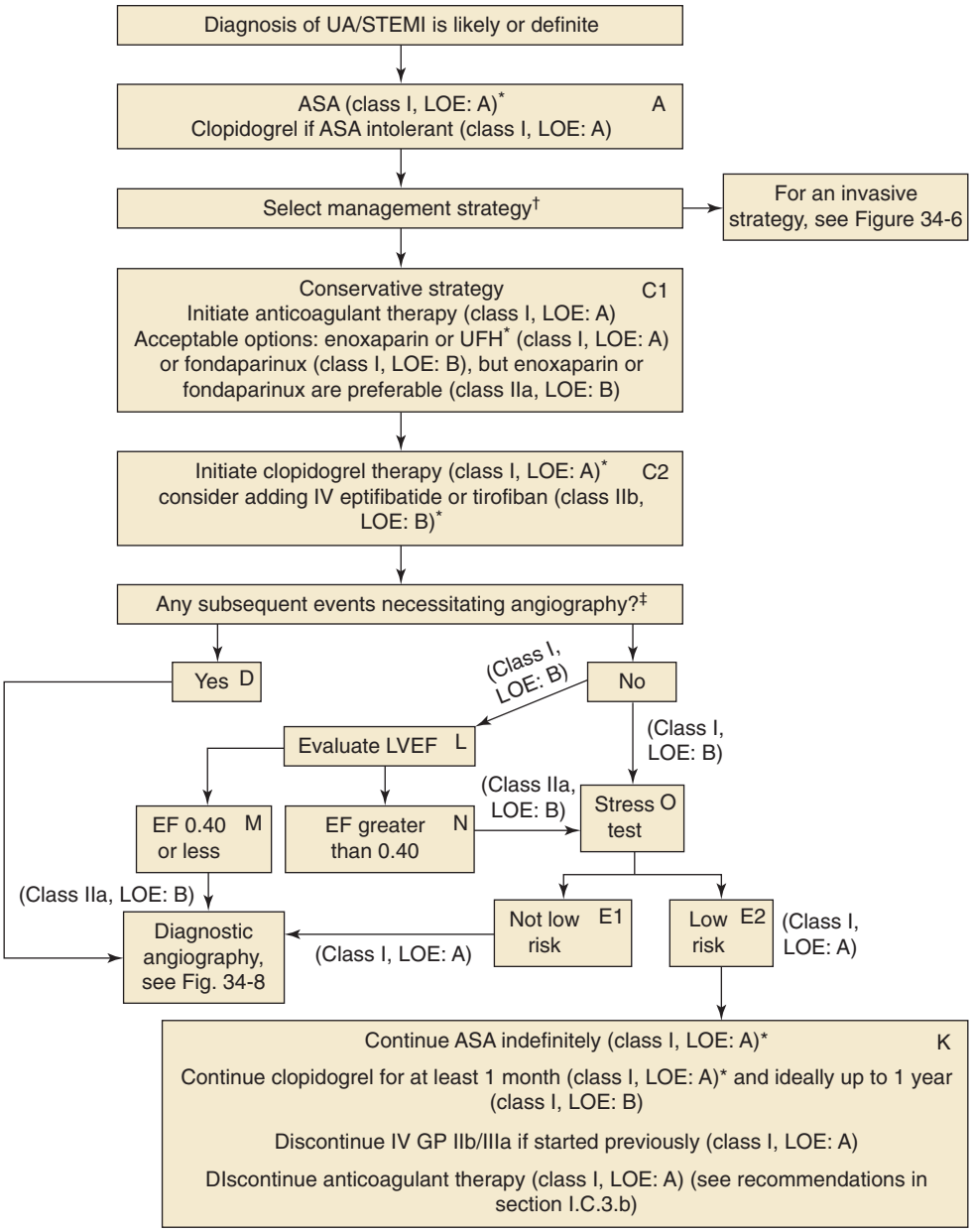


FIGURE 34–4 Algorithm for patients with UA/NSTEMI managed by an initial conservative strategy. ASA, aspirin, GP, glycoprotein, LOE, level of evidence, LVEF, left ventricular ejection fraction, UFH, unfractionated heparin. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

Prior meta-analyses have suggested that routine invasive therapy yields better long-term clinical outcomes in higher-risk patients.[33] In contrast, a relatively recent trial, ICTUS, has reported equivalent outcomes (and fewer biomarker MIs) with selective invasive therapy in stabilized but troponin-positive patients.[7,31] Proposed explanations for this result have included more aggressive medical therapy (statins, clopidogrel) than in previous studies, a high rate of revascularization in the selective invasive arm (47%), limited power for low event rates, and the counting of minor, clinically questionable troponin elevations as recurrent MIs. Longer-term (5 year) outcomes from two other, larger randomized trials: RITA-3[34] and FRISC-II,[35] published contemporaneously with ICTUS, favored the invasive strategy for the endpoint of death or nonfatal MI. A contemporary meta-analysis of 7 randomized trials, including ICTUS, continues to support the long-term benefit of an early invasive strategy, with a relative risk of all-cause mortality of 0.75 (95% confidence interval [CI], 0.63-0.90) and recurrent nonfatal MI of 0.83 (CI, 0.72-0.96).[6] Nevertheless, these guidelines recognize that an initially conservative (selective invasive) strategy may be considered (Class IIb, LOE B) as an alternative treatment option in stabilized UA/NSTEMI patients based on physician judgment and patient preference.[7]

In contrast to these results for higher-risk patients, for those at lower risk, especially lower-risk women, accumulating evidence favors an initial conservative strategy. For example, in TACTICS TIMI-18, there was a reduction in the composite risk of death, nonfatal MI, or rehospitalization for UA in women with intermediate (3 to 4) or high (5 to 7) TIMI risk scores undergoing an early invasive strategy that was similar to that in men.[10] In contrast, women with a low TIMI risk score had an increased risk of events (odds ratio [OR], 1.59; 95% CI, 0.69-3.67) with the invasive versus the

TABLE 34–2 Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

Preferred Strategy	Patient Characteristics
Invasive*	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Elevated cardiac biomarkers (TnT or TnI) New or presumably new ST-segment depression Signs or symptoms of HF or new or worsening mitral regurgitation High-risk findings from noninvasive testing Hemodynamic instability Sustained ventricular tachycardia PCI within 6 months Prior CABG High-risk score (e.g., TIMI, GRACE) Reduced left ventricular function (LVEF less than 40%)
Conservative	Low-risk score (e.g., TIMI, GRACE) Patient or physician preference in the absence of high-risk features

*The European guidelines[21] also recognize diabetes and renal dysfunction.

GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis In Myocardial Infarction; TnI, troponin I; TnT, troponin T.

Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.

conservative strategy, whereas low-risk men had similar outcomes with the two strategies. Similarly, women with an elevated troponin T benefited from an invasive strategy (adjusted OR, 0.47; 95% CI, 0.26-0.83), whereas the primary endpoint was significantly more frequent in women (but not men) treated invasively with a negative troponin (OR, 1.46; 95% CI, 0.78-2.72).[10] The FRISC-II[35] and RITA-3[9,34] randomized trials reported improved outcomes with an invasive strategy only in men, but a high percentage of women were low risk, and an assessment of outcomes by risk or troponin status was not reported. A more recently published meta-analysis also supports the recommendation favoring a conservative approach in low-risk women.[36]

Several criteria to consider in choosing between an invasive or conservative strategy are summarized in Table 34-2.

Selected Recommendations: Initial Conservative Versus Initial Invasive Strategies

Class I

1. An early invasive strategy (i.e., angiography with intent to perform revascularization) is indicated in patients with UA/NSTEMI who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). (*LOE: B*)
2. An early invasive strategy (i.e., angiography with intent to perform revascularization) is indicated in initially stabilized UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events. (*LOE: A*)
3. In women with low-risk features, a conservative strategy is recommended. (*LOE: B*) *(see also section on Women)*
4. Because of the many anatomic possibilities that might be responsible for recurrent ischemia, there should be a low threshold for angiography in post-coronary artery bypass graft (CABG) patients with UA/NSTEMI. (*LOE: C*) *(see also section on Post-CABG Patients)*

Class IIb

1. In initially stabilized patients, an initial conservative (i.e., selectively invasive) strategy may be considered for UA/NSTEMI patients who have an elevated risk for clinical events including those who are troponin positive. (*LOE: B*) The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made considering physician and patient preference. (*LOE: C*)
2. An invasive strategy may be reasonable in patients with chronic renal insufficiency. (*LOE: C*)

Class III

1. An early invasive strategy (i.e., angiography with intent to perform revascularization) is not recommended in patients with acute chest pain and a low likelihood of ACS. (*LOE: C*)

ANTIPLATELET THERAPY

Platelets represent a principal component of thrombus formation after plaque disruption precipitating ACS, and inhibition of platelet aggregation represents an essential element in UA/NSTEMI therapy.

Aspirin

Aspirin acts to inhibit cyclooxygenase (COX)-1 within platelets, prevent thromboxane A_2 formation, and diminish platelet aggregation associated with that pathway. Early trials of aspirin in UA/NSTEMI consistently documented benefit and established aspirin as a standard element of initial and chronic care. Higher doses are given for initiation of therapy and after stent placement followed by lower doses for long-term maintenance.

Platelet Glycoprotein (GP) IIb/IIIa Antagonists

Activation of platelets by a number of mechanisms leads to expression of GP IIb/IIIa receptors on their cell membranes that have high affinity for fibrinogen. The GP IIb/IIIa receptor antagonists (inhibitors) act by occupying these receptors, preventing fibrinogen binding, preventing platelet aggregation, and thereby reducing thrombus propagation. The three approved GP IIb/IIIa antagonists have differing properties. Abciximab, a humanized murine Fab antibody fragment, has strong receptor affinity and a short plasma half-life but a more prolonged (1 to 2 day) pharmacodynamic effect. Eptifibatide, a cyclic heptapeptide, and tirofiban, a nonpeptide fibrinogen mimetic, have high receptor specificity but short half-lives (2 to 3 hours) and short durations of antiplatelet effect (4 to 8 hours).

The efficacy of GP IIb/IIIa inhibitors for prevention of percutaneous coronary intervention (PCI)-related complications has been documented in several trials. The three trials most relevant to UA/NSTEMI are CAPTURE (abciximab),[37] PRISM-PLUS (tirofiban),[38] and PURSUIT (eptifibatide).[39] Each showed a significant reduction in rate of MI or death during the phase of medical management preceding intervention and an augmented benefit after PCI (each receives a Class I indication with an invasive strategy). In contrast, GP IIb/IIIa antagonist trials of patients with UA/NSTEMI not routinely scheduled to undergo coronary revascularization have suggested a more modest benefit (greater among patients with elevated troponin or ECG changes) for tirofiban and eptifibatide,[40] which receive a Class IIb indication, and no benefit or a suggestion of harm for abciximab (GUSTO-IV),[41] which receives a class III (contraindication) in conservatively (non-invasively) managed UA/NSTEMI patients.

Adenosine Diphosphate Receptor Antagonists

Ticlopidine and clopidogrel are adenosine diphosphate (ADP) purinergic G protein–coupled P2Y 12 (P2Y12) receptor antagonists currently approved for antiplatelet therapy. Their platelet effects are irreversible but take several hours to days to achieve maximal therapeutic effect, depending on whether and how large a loading dose is given. Because of a better safety profile, clopidogrel is generally preferred.

The CURE trial randomized 12,562 patients with UA/NSTEMI to clopidogrel (300 mg, then 75 mg/day) or placebo (plus aspirin) and followed them for 3 to 12 months.[42] Cardiovascular death, MI, or stroke occurred in 9.3% of clopidogrel and 11.5% of placebo patients (relative risk [RR] 0.80; $P < .001$). Benefit was observed across all subgroups and began within a few hours. A small bleeding excess was noted, which was increased in patients undergoing bypass surgery within 5 days of stopping clopidogrel. The 2658 patients undergoing PCI within the CURE trial (PCI-CURE substudy)[43] experienced a 30% reduction in cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI ($P = .03$) and a 31% reduction in cardiovascular death or MI ($P = .002$). Therefore, clopidogrel is indicated in UA/NSTEMI patients treated with either a conservative or an invasive strategy.

Combination and Timing of Antiplatelet Therapy

A challenge for current guidelines is the integration of the GP IIb/IIIa antagonist studies from the 1990s with more recent studies using clopidogrel and newer anticoagulants. The ISAR-REACT-2 trial tested whether patients undergoing PCI and preloaded with clopidogrel 600 mg at least 2 hours before the procedure would derive additional benefit from GP IIb/IIIa receptor antagonist therapy with abciximab, given at angiography. The study randomized 2022 patients with UA/NSTEMI to abciximab or placebo. The primary ischemic endpoint was reduced from 11.9% to 8.9% (RR, 0.75; CI, 0.58-0.97; $P = .03$). Benefit was limited to patients with an elevated troponin level. Thus, it appears that addition of a GP IIb/IIIa receptor antagonist to thienopyridine therapy is beneficial in patients undergoing an invasive strategy with high-risk features.

The timing of initiating clopidogrel and GP IIb/IIIa inhibitors in patients undergoing an invasive evaluation, however, is currently controversial. An argument for "upstream" initiation before angiography is that it may have incremental benefit to GP IIb/IIIa inhibition, with earlier initiation providing optimal benefit. An argument for delayed initiation of clopidogrel until the time of angiography is that patients with advanced CAD requiring bypass surgery are placed at higher bleeding risk for early surgery or must experience a 5- to 7-day delay to surgery to allow for elimination of antiplatelet effect, that intravenous (IV) GP IIb/IIIa inhibitor therapy is sufficiently protective until the time of early angiography, and that clopidogrel's effect is delayed for several hours after oral dosing. Clinical trials data are not definitive as to which strategy provides the better benefit-risk ratio, and the current guidelines allow for either approach, both of which are in current widespread use. The future availability of short-acting, rapidly reversible and intravenously administered ADP receptor antagonists (e.g., cangrelor) may allow resolution of these two divergent approaches. Another potent oral ADP receptor antagonist, prasugrel, has undergone favorable phase III clinical trials testing in comparison with clopidogrel in UA/NSTEMI and may need to be integrated into therapeutic algorithms in the near future.[44]

The guidelines currently specify the administration of at least one (Class I, LOE A) or both (Class IIa, LOE B) of these two classes of antiplatelet agents prior to angiography, with both upstream GP IIb/IIIa inhibitor and clopidogrel therapy being favored when there are delays to angiography, high-risk features, or early recurrent ischemic discomfort in invasively treated patients (see Fig. 34-3). In conservatively treated patients, early clopidogrel (Class I, LOE B) is recommended, with the consideration of adding eptifibatide or tirofiban (Class IIb, LOE B) in those with high-risk features (e.g., troponin elevation, ECG changes, recurrent ischemia) (see Fig. 34-4).

Selected Recommendations: Early Antiplatelet Therapy

Class I

1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant to that medication (*LOE: A*) (see Figs. 34-3 and 34-4, box A).
2. Clopidogrel (loading dose followed by daily maintenance dose)* should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (*LOE: A*) (see Figs. 34-3 and 34-4, box A).
3. In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly. (*LOE: B*)
4. For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an IV GP IIb/IIIa inhibitor (*LOE: A*) (see Fig. 34-3).

   Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred GP IIb/IIIa inhibitor. (*LOE: B*)
5. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, clopidogrel (loading dose followed by daily maintenance dose)* should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (*LOE: A*) and ideally up to 1 year (*LOE: B*) (see Fig. 34-4, box C2).
6. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms, ischemia, HF, or serious arrhythmias subsequently appear, diagnostic angiography should be performed (*LOE: A*) (see Fig. 34-4, box D). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; *LOE: A*) or clopidogrel (loading dose followed by daily maintenance dose; *LOE: A*)* should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). (*LOE: C*)

Class IIa

1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, aspirin, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography. (*LOE: C*)

*Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel may more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but additive efficacy and safety of higher oral loading doses have not been rigorously established.

2. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel (loading dose followed by daily maintenance dose)* and an IV GP IIb/IIIa inhibitor (*LOE: B*)†.

   Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of a GP IIb/IIIa inhibitor. (*LOE: B*)
3. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an IV GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier. (*LOE: B*)

Class IIb

For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. (*LOE: B*) (see Fig. 34-4, box C2)

Class III

Abciximab should not be administered to patients in whom PCI is not planned. (*LOE: A*)

ANTICOAGULANT THERAPY

Anticoagulant therapy is an essential part of ACS management. A combination of an anticoagulant together with aspirin and an additional antiplatelet agent has proved to be the most effective therapeutic regimen. Two newer anticoagulants, bivalirudin and fondaparinux, have become available since the previous guidelines were written and have been integrated into current treatment algorithms together with UFH and LMWH (see Figs. 34-3 and 34-4).

Unfractionated Heparin

UFH potentiates the action of circulating antithrombin, which inactivates thrombin, factor IXa, and factor Xa, preventing thrombus propagation. A relatively small database of older randomized trials forms the evidence base for the benefits of UFH in UA/NSTEMI.[45] These data suggest a reduction in early ischemic events in the short term, but reactivation of thrombosis ("rebound") often occurs after discontinuation. Advantages of UFH include its broad clinical experience, its rapid reversibility, its mostly nonrenal elimination, and the ability to titrate the intensity of therapy by measuring activated thromboplastin time (aPTT).

Low–Molecular-Weight Heparin

LMWH preparations are enriched for chains of fewer than 18 pentasaccharide units, which inactivate factor Xa but not thrombin. Hence they have greater anti-Xa activity and lesser antithrombin activity than UFH. Compared with UFH, LMWH has decreased binding to plasma proteins and endothelial cells and dose-independent clearance with a longer half-life. This results in more predictable and sustained anticoagulation with once- or twice daily subcutaneous (SC) administration without the need for laboratory monitoring. Differences among LMWH preparations suggest that each be treated as a separate therapeutic entity. Trials of dalteparin and nadroparin have reported similar rates of death or nonfatal MI compared with UFH, whereas enoxaparin was favored over UFH in five of six trials, driven primarily by a reduction in nonfatal MI. Meta-analysis of the two largest, primarily noninvasive, studies of enoxaparin versus UFH in UA/NSTEMI reported a 20% relative reduction in death/ischemic events.[46] However, with an early invasive strategy, outcomes with UFH and LMWH were similar.[47] Several trials have demonstrated that LMWH (enoxaparin) can be used in combination with GP IIb/IIIa inhibitor therapy with favorable results in patients with ACS.[47,48] Based on this evidence, enoxaparin (or fondaparinux) is preferred in the guidelines to UFH (Class IIa) in patients treated with an initial conservative strategy unless bypass surgery is scheduled within 24 hours.

Direct Thrombin Inhibitors

Hirudin, the prototype direct thrombin inhibitor, has been studied extensively but with mixed results, including excess bleeding with higher doses. More recently, bivalirudin, a synthetic analog of hirudin that binds reversibly to thrombin and inhibits clot-bound thrombin, has been developed and tested. Bivalirudin was studied in the ACUITY trial in 13,819 patients with UA/NSTEMI treated with an invasive strategy,[15] comparing it with a heparin (UFH or enoxaparin), with or without upstream GP IIb/IIIa inhibition, in a randomized but open-label 2 × 2 factorial design. Bivalirudin compared with a heparin gave noninferior 30-day rates of ischemic events (7.7% vs. 7.3%), major bleeding (5.3% vs. 5.7%), and net clinical outcomes (11.8% vs. 11.7%) when given with a GP IIb/IIIa inhibitor. Bivalirudin without a GP IIb/IIIa inhibitor resulted in comparable rates of ischemic events (7.0% vs. 7.3%) as a heparin plus a GP IIb/IIIa inhibitor in the subgroup of patients who received a thienopyridine (primarily clopidogrel) before angiography, PCI, or both, and resulted in lower bleeding rates. In contrast, it was inferior in patients who did not receive at least 300 mg of clopidogrel at least 6 hours prior to angiography (9.1% vs. 7.1%; RR, 1.29; CI, 1.03-1.63, *P* for interaction = .054) (Fig. 34-5). Thus, the guidelines indicate that a bivalirudin-based anticoagulation strategy is useful in UA/NSTEMI patients undergoing an invasive strategy if concomitant treatment is given with a GP IIb/IIIa inhibitor or clopidogrel, administered at least 6 hours before angiography. Because bivalirudin is renally cleared, dose adjustment is required with renal insufficiency.

Factor Xa Inhibitors

Factor Xa inhibitors act proximally in the coagulation cascade to suppress thrombin generation by inhibiting the multiplier effects of downstream reactions. Factor Xa inhibitors do not act against formed thrombin. Since the previous version of the guidelines, the pentasaccharide factor Xa inhibitor fondaparinux has been developed and tested as an anticoagulant in ACS. Fondaparinux demonstrates slow and dose-independent renal clearance, allowing it to be administered as a fixed-dose, once-daily subcutaneous dose without laboratory monitoring. Fondaparinux (2.5 mg SC daily) was tested by the OASIS-5 investigators in comparison with enoxaparin (1 mg/kg SC twice daily) in 20,078 patients with UA/NSTEMI in a randomized, double-blinded study.[14] The primary outcome of death, MI, or refractory ischemia at 9 days was similar (noninferior) with fondaparinux (5.8% vs. 5.7%) with lower rates of major bleeding (2.2% vs. 4.1%, $P < .001$) (Fig. 34-6). Longer follow-up favored the fondaparinux group, including lower 6-month rates of death (5.8% vs. 6.5%) and death, MI, or stroke (11.3% vs. 12.5%).

An early observation in OASIS-5 was an increased rate of catheter-related thrombosis, which led to a protocol amendment permitting the use of open-label UFH at the

*Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel may more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but additive efficacy and safety of higher oral loading doses have not been rigorously established.

†Factors favoring the administration of both clopidogrel and a GP IIb/IIIa inhibitor include: delay to angiography, high-risk features, and early recurrent ischemic discomfort.

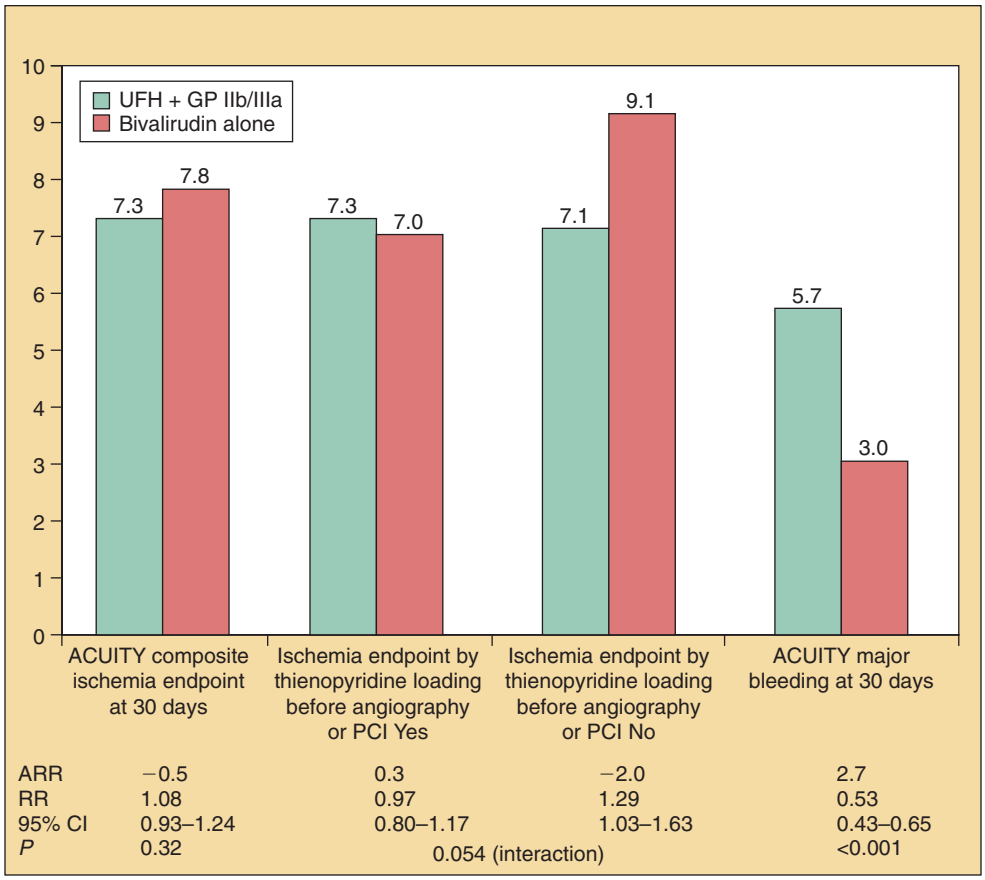


FIGURE 34–5 ACUITY Study composite ischemic and bleeding outcomes at 30 days. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

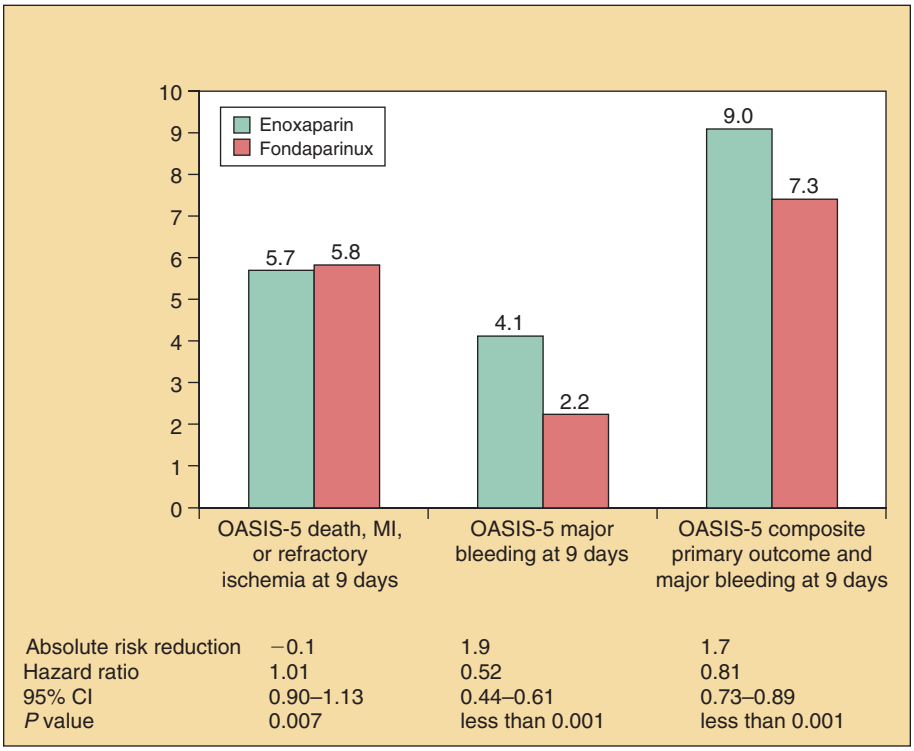


FIGURE 34–6 OASIS-5 Study cumulative risks of ischemic and bleeding events at 9 days. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

investigator's discretion later in the study for patients undergoing angiography. Additional concerns about the utility of fondaparinux with an invasive approach were raised by its inferior performance in patients with STEMI undergoing primary PCI in the OASIS-6 trial.[49] Thus, an antithrombin (e.g., UFH, 50-60 U/kg IV) is recommended if fondaparinux has been chosen as the anticoagulant and the patient undergoes angiography/PCI.

In contrast to its confounded use for an invasive strategy, fondaparinux appears to represent a preferred anticoagulant strategy in those at higher bleeding risk managed with a noninvasive strategy, for which the guidelines give a Class I (LOE B) indication. The guidelines also give a Class IIa (LOE B) preference to fondaparinux (and enoxaparin) over UFH in general for patients treated with an initial conservative strategy unless bypass surgery is scheduled within 24 hours.

Selected Recommendations: Anticoagulant Therapy

Class I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

1. For patients in whom an invasive strategy is selected, regimens with established efficacy at a *LOE: A* include enoxaparin and UFH (see Fig. 34-3, box B1), and those with established efficacy at a *LOE: B* include bivalirudin and fondaparinux (see Fig. 34-3, box B1).
2. For patients in whom an initial conservative strategy is selected, regimens using either enoxaparin* or UFH (*LOE: A*) or fondaparinux (*LOE: B*) have established efficacy (see Fig. 34-4, box C1).* See also class IIa recommendation below.
3. In patients in whom an initial conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable (*LOE: A*) (see Fig. 34-4, box C1).

Class IIa

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin* or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG surgery is planned within 24 hours. (*LOE: B*)

CORONARY REVASCULARIZATION

Coronary revascularization with PCI or CABG is performed with the intent to improve prognosis, relieve symptoms, prevent ischemic complications, and increase functional capacity. Indications and selection criteria for revascularization by PCI or CABG in UA/NSTEMI are generally similar to those for patients with stable angina as detailed in guidelines for chronic stable angina and PCI, both recently updated.[50,51]

In recent years, PCI outcomes have improved with the use of stents, including drug-eluting stents, improved associated technologies, and the use of improved antiplatelet and anticoagulant regimens. Similarly, surgical techniques and outcomes have improved. Published success rates in UA/NSTEMI patients are high with contemporary approaches with both modalities. A New York registry of patients revascularized in the 1990s reported lower adjusted long-term mortality rates in five advanced anatomic subsets with CABG compared with PCI.[52] Recent randomized comparisons of PCI and CABG, however, have reported comparable survival rates (e.g., AWESOME and ARTS trials).[53,54] A meta-analysis of four trials of CABG versus PCI with bare-metal stenting for multivessel disease between 1995 and 2000 similarly reported no difference in death, MI, and stroke, or in death alone.[55]

Both PCI and CABG have evolved in the past few years, and no published trials adequately reflect current interventional techniques. Drug-eluting stents carry a slightly higher risk of late stent thrombosis but without a negative impact on overall ischemic events.[56] Considering total experience to date, it is reasonable to consider CABG to be a preferred revascularization strategy for most patients with three-vessel disease, especially if it involves the proximal left anterior descending (LAD) coronary artery, and for patients with multivessel disease and diabetes mellitus or LV dysfunction (Fig. 34-7). However, while awaiting additional clinical trials information, it seems unwise to deny contemporary PCI to individual patients in some of these subsets (e.g., diabetics with less severe CAD).

Selected Recommendations: Coronary Revascularization

A. Percutaneous Coronary Intervention

Class I

1. An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious comorbidity and who have coronary lesions amenable to PCI and any of the high-risk features.
2. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with one- or two-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*LOE: B*)
3. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. (*LOE: A*)
4. An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI (*LOE: A*) (see Figs. 34-3 and 34-4).

Class IIa

1. Percutaneous coronary intervention is reasonable for focal saphenous vein graft (SVG) lesions or multiple stenoses in UA/NSTEMI patients who are undergoing medical therapy and who are poor candidates for reoperative surgery. (*LOE: C*)
2. Percutaneous coronary intervention (or CABG) is reasonable for UA/NSTEMI patients with one- or two-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. (*LOE: B*)
3. Percutaneous coronary intervention (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with one-vessel disease with significant proximal left anterior descending CAD. (*LOE: B*)
4. Use of PCI is reasonable in patients with UA/NSTEMI with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG or who require emergent intervention at angiography for hemodynamic instability. (*LOE: B*)

Class IIb

1. In the absence of high-risk features associated with UA/NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who are undergoing medical therapy and who have one or more lesions to be dilated with a reduced likelihood of success. (*LOE: B*)

*Limited data are available for the use of other LMWHs (e.g., dalteparin) in UA/NSTEMI.

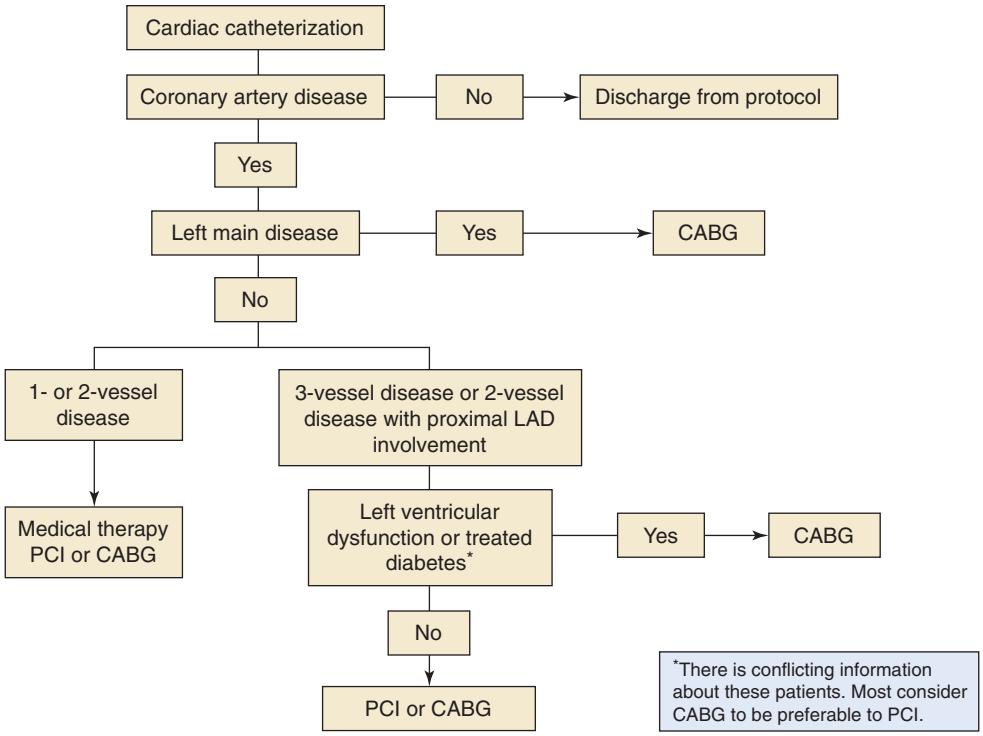


FIGURE 34–7 Selection of revascularization strategy in UA/NSTEMI. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

2. Percutaneous coronary intervention may be considered for UA/NSTEMI patients who are undergoing medical therapy who have two- or three-vessel disease, significant proximal left anterior descending CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy. (*LOE: B*)

Class III

1. Percutaneous coronary intervention (or CABG) is not recommended for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (*LOE: C*)
2. In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have one or more of the following:
   a. Only a small area of myocardium at risk. (*LOE: C*)
   b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. (*LOE: C*)
   c. A high risk of procedure-related morbidity or mortality. (*LOE: C*)
   d. Insignificant disease (less than 50% coronary stenosis). (*LOE: C*)
   e. Significant left main CAD and candidacy for CABG. (*LOE: B*)
3. A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated. (*LOE: B*)

B. Coronary Artery Bypass Graft (CABG)

Class I

1. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with significant left main CAD (greater than 50% stenosis). (*LOE: A*)
2. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with three-vessel disease; the survival benefit is greater in patients with abnormal LV function (LVEF less than 0.50). (*LOE: A*)
3. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with two-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (LVEF less than 0.50) or ischemia on noninvasive testing. (*LOE: A*)
4. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients in whom percutaneous revascularization is not optimal or possible and who have ongoing ischemia not responsive to maximal nonsurgical therapy. (*LOE: B*)
5. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with one- or two-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*LOE: B*)
6. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. (*LOE: A*)

Class IIa

1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes. (*LOE: B*)
2. It is reasonable to perform CABG with the internal mammary artery for UA/NSTEMI patients with multivessel disease and treated diabetes mellitus. (*LOE: B*)
3. Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is

significant stenosis of a graft that supplies the LAD coronary artery. (*LOE: C*)

4. Coronary artery bypass graft surgery (or PCI) is reasonable for UA/NSTEMI patients with one- or two-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. (*LOE: B*)
5. Coronary artery bypass graft surgery (or PCI) can be beneficial compared with medical therapy for UA/NSTEMI patients with one-vessel disease with significant proximal left anterior descending CAD. (*LOE: B*)
6. Coronary artery bypass graft surgery (or PCI with stenting) is reasonable for patients with multivessel disease and symptomatic myocardial ischemia. (*LOE: B*)

Class IIb

Coronary artery bypass graft surgery may be considered in patients with UA/NSTEMI who have one- or two-vessel disease not involving the proximal LAD with a modest area of ischemic myocardium when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria on noninvasive testing, this recommendation becomes a class I recommendation.) (*LOE: B*)

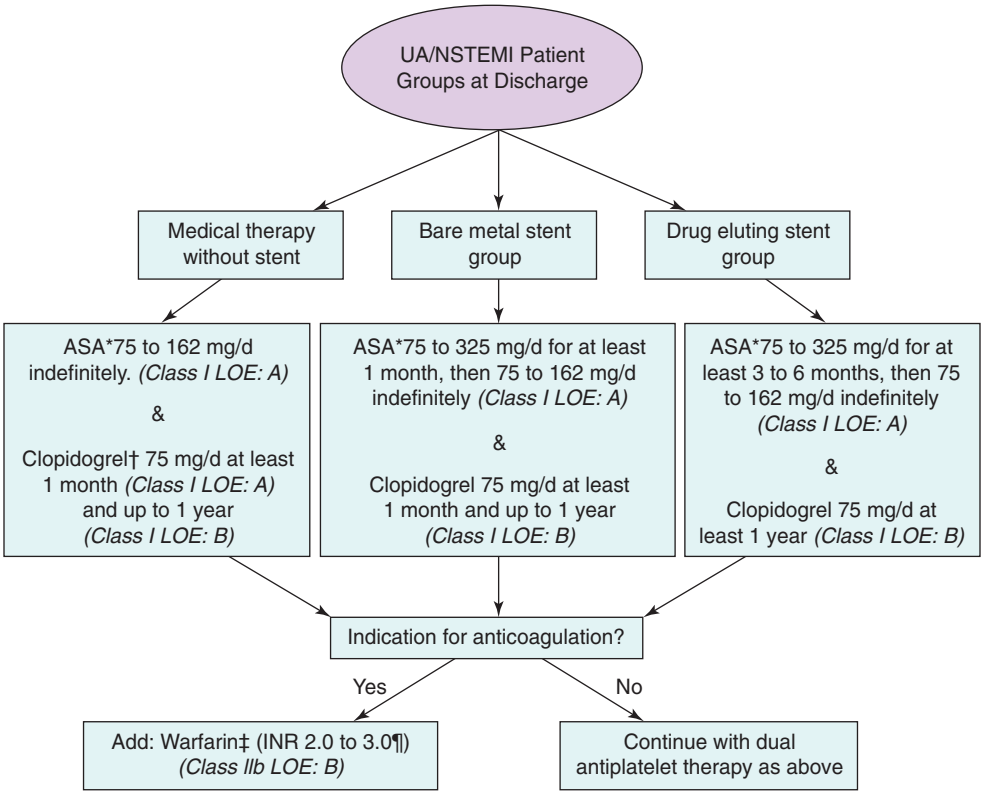
Class III

Coronary artery bypass graft surgery (or PCI) is not recommended for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (*LOE: C*)

LATE HOSPITAL CARE, HOSPITAL DISCHARGE, AND POSTHOSPITAL DISCHARGE CARE

General Principles and Care Objectives

The two principal goals in preparing for hospital discharge are the following: (1) to prepare the patient to return to as near normal activity as possible; and (2) to use the acute event as a teaching opportunity to emphasize appropriate lifestyle modifications and aggressive risk factor reduction. A multidisciplinary health care team is ideal to accomplish these objectives. Oral anti-ischemic, antiplatelet, and secondary preventive medications used in the nonintensive phase of hospitalization are generally continued after discharge (Fig. 34-8; Table 34-3). Educational efforts should focus



* For aspirin (ASA)-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.
† For clopidogrel-allergic patients, use ticlopidine, 250 mg PO bid.
‡ Discontinue clopidogrel 1 month after implantation of a bare metal stent, 3 months after a sirolimus stent, and 6 months after a paclitaxel stent because of the potential increased risk of bleeding with warfarin and two antiplatelet agents. Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; cerebral, venous, or pulmonary emboli.
¶An INR of 2.0 to 3.0 is acceptable with tight control, but the lower end of this range is preferable while given with ASA and clopidogrel, especially in older patients and those with other risk factors for bleeding.
d indicates day; INR, international normalized ratio.

FIGURE 34–8 Long-term antithrombotic therapy after UA/NSTEMI. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.)*

TABLE 34–3 Medication Used for Stabilized Unstable Angina/Non–ST-Segment Elevated Myocardial Infarction Patients

Anti-Ischemic and Antithrombotic/Antiplatelet Agents	Drug Action	Class/Level of Evidence
Aspirin	Antiplatelet	I/A
Clopidogrel* or ticlopidine	Antiplatelet when aspirin is contraindicated	I/A
Beta blockers	Anti-ischemic	I/B
ACEI	EF less than 0.40 or HF EF greater than 0.40	I/A IIa/A
Nitrates	Antianginal	I/C for ischemic symptoms
Calcium antagonists (short-acting dihydropyridine antagonists should be avoided)	Antianginal	I for ischemic symptoms; when beta blockers are not successful (B) or contraindicated, or cause unacceptable side effects (C)
Dipyridamole	Antiplatelet	III/A

Agents for Secondary Prevention and Other Indications	Risk Factors	Class/Level of Evidence
HMG-CoA reductase inhibitors	LDL cholesterol >100 mg/dL LDL cholesterol >70 mg/dL	I/A Ia/A
Fibrates	HDL cholesterol <40 mg/dL	IIa/B
Niacin	HDL cholesterol <40 mg/dL	IIa/B
Niacin or fibrate	Triglycerides 200 mg/dL	IIa/B
Antidepressant	Treatment of depression	IIb/B
Treatment of hypertension	Blood pressure higher than 140/90 mm Hg or higher than 130/80 mm Hg if kidney disease or diabetes present	I/A
Hormone therapy (initiation)†	Postmenopausal state	III/A
Treatment of diabetes	HbA_{1C} greater than 7%	I/B
Hormone therapy (initiation)†	Postmenopausal state	III/B
COX-2 inhibitor or NSAID	Chronic pain	IIa/C IIb/C or III/C
Vitamins C, E, beta-carotene; folic acid, B_6, B_{12}	Antioxidant effect; homocysteine lowering	III/A

*Preferred to ticlopidine.

†For risk reduction of coronary artery disease.

ACEI, angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; HMG-CoA, hydroxymethylglutaryl coenzyme A; INR, international normalized ratio.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116:e148-e304.

on understanding of and targets for low-density lipoprotein cholesterol (LDL)-C and high-density lipoprotein cholesterol (HDL)-C, blood pressure, diabetes mellitus, diet, and weight management.[20,57]

Oral Antiplatelet Therapy

Aspirin should be administered in maintenance doses (75-162 mg daily) indefinitely to all UA/NSTEMI patients without contraindications. Higher doses (162-365 mg daily) are recommended for 1 month (bare-metal stents) or 3 to 6 months (drug-eluting stents) after PCI with stenting. ADP receptor blockade has played a critical role in reducing the risk of stent thrombosis as well as the risk of incident ischemic events after medical therapy for UA/NSTEMI, as summarized earlier in the section on antiplatelet therapy. Increased awareness of late (at >3-6 months) stent thrombotic events, believed to be associated with delayed endothelialization of drug-eluting stents, and the observation of increased risk of thrombotic events with premature drug discontinuation,[17] have led to revised recommendations on the duration of clopidogrel therapy (see Fig. 34-8). Clopidogrel (75 mg/d) is recommended for at least 1 month and ideally up to 1 year after medical therapy alone or after placing a bare-metal stent (BMS), and for at least 1 year after drug-eluting stent (DES) placement. Few data are available to inform recommendations about warfarin use in combination with antiplatelet therapy, and current recommendations are based on limited observational data and consensus opinion (see Fig. 34-8).

Lifestyle and Secondary Preventive Measures

There is a wealth of evidence that lowering elevated LDL-C reduces vascular events in patients with CAD. Indeed, there is mounting evidence that statin therapy is beneficial regardless of baseline LDL-C levels and is safe.[58,59] Accordingly, the guidelines present alternative Class I recommendations for predischarge statin therapy, which are as follows: (1) initiate and guide therapy based on measured LDL-C levels and targets (<100 mg/dL target = I/A, <70 mg/dL = IIa/A) (see Table 34-3), the traditional approach; or (2) initiate in all UA/NSTEMI regardless of baseline LDL-C.

Whereas ACE inhibitors, or angiotensin receptor blockers, are indicated in those with heart failure or reduced left ventricular function, data on their utility in stable CAD without LV dysfunction is controversial. This conflict can be resolved by considering the benefit across the CAD spectrum to be proportional to risk, with those at lowest risk benefiting least and those at greatest risk benefiting most.[60] Aldosterone receptor blockade is now recognized to provide incremental benefit when added to ACE inhibitors in patients with heart failure and depressed ejection fraction after MI[61] and is recommended for long-term therapy unless contraindicated.

Patients with elevated blood pressure should be educated and motivated to achieve normotension. Lower targets are appropriate for those with diabetes and chronic kidney disease. Tobacco cessation has substantial potential to improve survival in those who smoke, and additional smoking cessation aids are now available.[62] Overweight patients should be instructed in a weight loss regimen, emphasizing regular exercise and a lifelong prudent diet to achieve and maintain ideal body mass index.[63] The use of NSAIDs other than aspirin and COX-2-selective inhibitors should be minimized in UA/NSTEMI patients because of an increase in cardiovascular risk.[12,64] Folic acid/B-vitamin and supplementation with antioxidant vitamins (C, E) has not shown to be beneficial in clinical trials and is not recommended for secondary prevention.[57] Similarly, because of the potential for increased risk, hormone therapy with estrogen with or without a progestin should not be initiated in women after UA/NSTEMI.[57]

Regular physical activity usually may begin within 1 to 2 weeks after revascularized UA/NSTEMI (restrictions apply with residual ischemia), and daily walking may begin immediately. Cardiac rehabilitation can improve exercise tolerance and has shown promising results on outcomes. In stable patients, sexual activity with the usual partner may be resumed within 7 to 10 days, driving within 1 week, and air travel after 2 weeks. After complicated MI, driving should be delayed until 2 to 3 weeks after symptoms have resolved, whereas in low-risk, revascularized patients, return to work, driving, flying, and other normal activities may be accelerated (often to within a few days). Return to work depends on multiple factors in addition to cardiac functional status. However, recommending a return to work at 2 weeks in low-risk patients appears to be safe.[65]

Selected Recommendations: Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care

A. Medical Regimen and Use of Medications

Class I

1. All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. (*LOE: C*)
2. If the pattern or severity of anginal symptoms changes, which suggests worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or now occurs at rest), the patient should contact his or her physician without delay to assess the need for additional treatment or testing. (*LOE: C*)

B. Long-Term Medical Therapy and Secondary Prevention

i. Antiplatelet therapy (see Fig. 34-8)

Class I

1. For UA/NSTEMI patients treated medically without stenting, aspirin* (75 to 162 mg per day) should be prescribed indefinitely. (*LOE: A*); clopidogrel† (75 mg per day) should be prescribed for at least 1 month (*LOE: A*) and ideally for up to 1 year (*LOE: B*)
2. For UA/NSTEMI patients treated with PCI with BMS, aspirin* 162 to 325 mg per day should be prescribed for at least 1 month (*LOE: B*), then continued indefinitely at a dose of 75 to 162 mg per day. (*LOE: A*); clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding, then it should be given for a minimum of 2 weeks). (*LOE: B*)
3. For UA/NSTEMI patients treated with PCI with DES, aspirin* 162 to 325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation (*LOE: B*), then continued indefinitely at a dose of 75 to 162 mg per day. (*LOE: A*). Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES (*LOE: B*)
4. Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors). (*LOE: A*)

ii. Beta Blockers

Class I

1. Beta blockers are indicated for all patients recovering from UA/NSTEMI unless contraindicated. (For those at low risk, see Class IIa recommendation below). Treatment should begin within a few days of the event, if not initiated acutely, and should be continued indefinitely. (*LOE: B*)
2. Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme. (*LOE: B*)

Class IIa

It is reasonable to prescribe beta blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications. (*LOE: B*)

iii. Inhibition of the Renin-Angiotensin-Aldosterone System

Class I

1. Angiotensin-converting enzyme inhibitors should be given and continued indefinitely for patients recovering from UA/NSTEMI with HF, LV dysfunction (ejection fraction less than 0.40), hypertension, or diabetes mellitus unless contraindicated. (*LOE: A*)
2. An angiotensin receptor blocker should be prescribed at discharge to those UA/NSTEMI patients who are intolerant of an ACE inhibitor and who have either clinical or radiologic signs of HF and LVEF less than 0.40. (*LOE: A*)
3. Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated creatinine clearance should be greater than 30 mL/min) or hyperkalemia (potassium should be less than or equal to 5 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic HF or diabetes mellitus. (*LOE: A*)

Class IIa

1. Angiotensin-converting enzyme inhibitors are reasonable for patients recovering from UA/NSTEMI in the absence of LV dysfunction, hypertension, or diabetes mellitus unless contraindicated. (*LOE: A*)
2. Angiotensin-converting enzyme inhibitors are reasonable for patients with HF and LVEF greater than 0.40. (*LOE: A*)
3. In UA/NSTEMI patients who do not tolerate ACE inhibitors, an angiotensin receptor blocker can be useful as an alternative to ACE inhibitors in long-term management provided there are either clinical or radiologic signs of HF and LVEF less than 0.40. (*LOE: B*)

iv. Nitroglycerin

*Short-acting dihydropyridine calcium channel blockers should be avoided.

Class I
1. Nitroglycerin to treat ischemic symptoms is recommended. (*LOE: C*)

v. Calcium Channel Blockers

Class I
1. Calcium channel blockers* are recommended for ischemic symptoms when beta blockers are not successful. (*LOE: B*)
2. Calcium channel blockers* are recommended for ischemic symptoms when beta blockers are contraindicated or cause unacceptable side effects. (*LOE: C*)

vi. Lipid Management

Class I
1. The following lipid recommendations are beneficial:
   a. Hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins), in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-UA/NSTEMI patients, including postrevascularization patients. (*LOE: A*)
   b. For hospitalized patients, lipid-lowering medications should be initiated before discharge. (*LOE: A*)
   c. For UA/NSTEMI patients with elevated LDL-C (greater than or equal to 100 mg per dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C of less than 100 mg per dL (*LOE: A*). Further titration to less than 70 mg per dL is reasonable. (*Class IIa, LOE: A*)
   d. Therapeutic options to reduce non-HDL-C are recommended, including more intense LDL-C–lowering therapy. (*LOE: B*)
   e. Dietary therapy for all patients should include reduced intake of saturated fats (to less than 7% of total calories), cholesterol (to less than 200 mg per day), and trans fat (to less than 1% of energy). (*LOE: B*)
   f. Promoting daily physical activity and weight management are recommended. (*LOE: B*)

Class IIb

Encouraging consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g per day) for risk reduction may be reasonable. For treatment of elevated triglycerides, higher doses (2 to 4 g/day) may be used for risk reduction. (*LOE: B*)

vii. Blood Pressure Control

Class I

Blood pressure control according to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines is recommended (i.e., blood pressure less than 140/90 mm Hg or less than 130/80 mm Hg if the patient has diabetes mellitus or chronic kidney disease). (*LOE: A*)

viii. Diabetes Mellitus

Class I

Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal hemoglobin A1c level of less than 7% (*LOE: B*). Diabetes management should also include the following:
1. Vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management) as recommended should be initiated and maintained. (*LOE: B*)
2. It is useful to coordinate the patient's diabetic care with the patient's primary care physician or endocrinologist. (*LOE: C*)

ix. Smoking Cessation

Class I

Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home are recommended. Follow-up referral to special programs or pharmacotherapy (including nicotine replacement) is useful as is adopting a stepwise strategy aimed at smoking cessation (the 5 A's: Ask, Advise, Assess, Assist, and Arrange). (*LOE: B*)

x. Weight Management

Class I

Weight management, as measured by body mass index and/or waist circumference, should be assessed on each visit. A body mass index of 18.5 to 24.9 kg/m^2 and a waist circumference (measured horizontally at the iliac crest) of less than 40 inches for men and less than 35 inches for women is recommended. (*LOE: B*)

xi. Physical Activity

Class I
1. The patient's risk after UA/NSTEMI should be assessed on the basis of an in-hospital determination of risk. A physical activity history or an exercise test to guide initial prescription is beneficial. (*LOE: B*)

xii. Depression

Class IIa

It is reasonable to consider screening UA/NSTEMI patients for depression and refer or treat when indicated. (*LOE: B*)

xiii. Cardiac Rehabilitation

Class I

Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and those moderate- to high-risk patients in whom supervised or monitored exercise training is warranted. (*LOE: B*)

*Short-acting dihydropyridine calcium channel blockers should be avoided.

SPECIAL GROUPS

The current guidelines contain an expanded section on 11 subgroups of UA/NSTEMI patients with special diagnostic and therapeutic considerations. A detailed review of these is beyond the scope of this chapter, but a few highlights of five of the groups follow.

Women

Women present at an older age and with more atypical features than men but constitute a considerable proportion of the UA/NSTEMI population. When adjustment is made for age, body size, and comorbidities, current evidence indicates that sex is not an independent risk factor for adverse outcomes. Management also is generally similar regardless of sex. Women derive similar treatment benefits as men from aspirin, clopidogrel, anticoagulants, beta blockers, ACE inhibitors, and statins. However, women experience higher rates of dosing errors and subsequent bleeding with antiplatelet and anticoagulant therapy.[66] Appropriate dose adjustments based on creatinine clearance (Cockroft-Gault formula), weight, and age, where recommended, can reduce this risk. Also, adjusted outcomes after PCI and CABG have improved and now are approaching those of men. As with men, high-risk women (e.g., by positive troponin or TIMI risk-score) with UA/NSTEMI benefit from an early invasive strategy. In contrast, low-risk women do not benefit and may be harmed by an invasive approach and aggressive medication strategies, whereas in low-risk men, outcomes from invasive and initial conservative strategies are similar.[9,10,40] This finding may relate to the higher percentage of low-risk women found to have obstructive CAD coupled with a higher rate of complications from aggressive medical and interventional procedures in women. Hence, an initial conservative strategy is preferred in low-risk women.

Diabetes Mellitus

Diabetic patients account for approximately one quarter of UA/NSTEMI patients, and CAD accounts for three quarters of deaths in diabetics. Further, diabetic patients have more severe and diffuse CAD, more vascular comorbidities, and are at higher risk of death, MI, and recurrent ischemia. Moreover, diagnosis is made more difficult by diabetic autonomic neuropathy, which frequently results in atypical or "silent" presentations. An advantage of CABG over balloon PCI in diabetics was noted in the BARI[67] and CABRI studies but not in some contemporary registries[68] where physician judgment in patient selection for PCI was operative. Moreover, PCI with stents, including DESs, and the use of GP IIb/IIIa antagonists have improved the outcome of diabetics undergoing PCI. Indeed, the benefits of GP IIb/IIIa inhibitors appear to be enhanced in patients with diabetes mellitus. Thus, although CABG remains a preferred revascularization approach in diabetics with extensive disease (see Fig. 34-7), ongoing trials are anticipated to provide important new insights in the near future on the relative merits of contemporary PCI versus CABG in various diabetic subgroups.

Both in-hospital hyperglycemia and hypoglycemia increase risk. Ideal treatment goals in the first 2 days remain to be established, but a preprandial glucose target of less than 110 mg/dL and a maximum daily target of less than 180 mg/dL are generally recommended after stabilization. Goals of chronic glycemic management follow those of the American Diabetic Association.

Post-CABG Patients

Approximately 20% of UA/NSTEMI patients have had previous CABG, and approximately 20% of CABG patients develop UA/NSTEMI over a 7.5-year follow-up. Also, post-CABG patients who develop UA/NSTEMI generally have more advanced coronary disease, have had more MIs, have greater LV dysfunction, are more often diabetic, and are at higher risk of complications than other patients. Given the complexity of disease and multiple anatomic possibilities that might be responsible for recurrent ischemia in post-CABG patients, there should be a low threshold for angiographic assessment. Revascularization with either reoperation or PCI, preferably with stenting, may be considered. When possible, PCI of a native vessel is preferred to PCI of a saphenous vein graft, which is fraught with the risk of PCI-related complications.

Older Adults

The terms *elderly* or *older adults* are often used to refer to those aged 75 years or older. These older adults account for more than one third of UA/NSTEMI patients and present with special challenges. They present more often with atypical symptoms (e.g., dyspnea), altered cardiovascular physiology, reduced renal function, increased comorbidities, and are at both greater disease risk and greater treatment risk. Fortunately, for most therapies, older subgroups experience benefits similar to those of younger age groups. Nevertheless, community-based registry information has indicated a high rate of excessive drug dosing in elderly UA/NSTEMI patients: 38% for UFH, 17% for LMWH, and 65% for GP IIb/IIIa antagonists[69]; 15% of excessive bleeding could be attributed to excessive dosing.[66] PCI can be successfully performed in elderly patients, and operative morbidity and mortality rates, although higher, have improved in recent years. An early invasive strategy conferred a large reduction in ischemic events (10.8% vs. 21.6%) in elderly patients in the TACTICS TIMI-18 trial but at the expense of an increased risk of major bleeding events (16.6% vs. 6.5%).[70] Thus, selection of older patients for an early invasive strategy and aggressive ancillary medical therapies requires clinical judgment and individual application. However, age alone should not preclude an invasive strategy.

Chronic Kidney Disease

Chronic kidney disease (CKD) is a potent risk factor for cardiovascular disease, qualifies as a coronary risk equivalent, and is a major risk factor for adverse outcomes after MI, including NSTEMI. Despite this, little is known about the optimal approach to UA/NSTEMI patients with CKD because of their underrepresentation or even exclusion from randomized controlled trials.[71] Limited evidence suggests that, appropriately monitored, generally recommended medications and strategies can be safely applied in CKD patients. However, bleeding risk is higher, at least in part because of intrinsic platelet dysfunction and dosing errors.[19] Renin-angiotensin-aldosterone inhibitors can pose a greater risk of hyperkalemia and worsening renal function in the CKD setting, and angiography carries a higher risk of contrast-induced nephropathy. PCI carries a higher rate of early and late complications.[71] Thus, in contrast to other high-risk subsets, the value of aggressive therapeutic interventions is less certain and in need of further study.

An assessment of renal function is critical to proper medical therapy of UA/NSTEMI, as many cardiovascular drugs are renally cleared (e.g., LMWH, bivalirudin, fondaparinux, short-acting GP IIb/IIIa inhibitors, etc.). Their doses should be adjusted for estimated creatinine clearance. The Cockroft-Gault formula is preferred for estimating creatinine clearance for this purpose because of its use in most clinical trials and in label dosing recommendations.

In patients with CKD undergoing angiography, isosmolar contrast media were designated as preferred agents in the 2007 guidelines based on evidence to the date of that writing. Subsequently, a randomized, double-blind trial, CARE, has been published comparing the low-osmolality contrast medium iopamidol with the isosmolality contrast medium iodixanol in 414 patients at high risk for contrast-induced nephropathy (GFR, 20 to 59 mL/min) undergoing coronary angiography or PCI.[72] Results suggested generally comparable outcomes: serum creatinine (SCr) increased more than or equal to 0.5 mg/dL in 4.4% of patients after iopamidol and 6.7% after iodixanol ($P = .39$); increases more than or equal to 25% occurred in 9.8% versus 12.4%, respectively ($P = .44$). Mean SCr increases were slightly less after iopamidol (0.07 vs. 0.12 mg/dL, $P = .03$). Results were consistent in the subgroup with diabetes. Based on CARE, it appears reasonable to consider using low-osmolality contrast (i.e., iopamidol) as well as isosmolality agent(s) when performing angiography or PCI in the setting of CKD.

Selected Recommendations: Special Groups

A. Women
   Class I
   1. Women with UA/NSTEMI should be managed with the same pharmacologic therapy as men both in the hospital and for secondary prevention, with special attention to antiplatelet and anticoagulant doses based on weight and renal function; doses of renally cleared medications should be based on estimated creatinine clearance. (*LOE: B*)
   2. In women with low-risk features, a conservative strategy is recommended. (*LOE: B*)

B. Diabetes Mellitus
   Class I
   1. Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization should be similar

in patients with and without diabetes mellitus. (*LOE: A*)
2. An intravenous platelet GP IIb/IIIa inhibitor should be administered for patients with diabetes mellitus as recommended for all UA/NSTEMI patients. (*LOE: A*). The benefit may be enhanced in patients with diabetes mellitus. (*LOE: B*)

Class IIa
1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes mellitus. (*LOE: B*)

C. Post-CABG Patients

Class I
1. Medical treatment for UA/NSTEMI patients after CABG should follow the same guidelines as for non–post-CABG patients with UA/NSTEMI. (*LOE: C*)
2. Because of the many anatomic possibilities that might be responsible for recurrent ischemia, there should be a low threshold for angiography in post-CABG patients with UA/NSTEMI. (*LOE: C*)

D. Older Adults

Class I
1. Older patients with UA/NSTEMI should be evaluated for appropriate acute and long-term therapeutic interventions in a similar manner as younger patients with UA/NSTEMI. (*LOE: A*)
2. Special attention should be given to appropriate dosing of pharmacologic agents (i.e., adjusted by weight and estimated creatinine clearance) in older patients with UA/NSTEMI because they often have altered pharmacokinetics (due to reduced muscle mass, renal and/or hepatic dysfunction, and reduced volume of distribution) and pharmacodynamics (increased risks of hypotension and bleeding). (*LOE: B*)

E. Chronic Kidney Disease

Class I
1. Creatinine clearance should be estimated in UA/NSTEMI patients, and the doses of renally cleared drugs should be adjusted appropriately. (*LOE: B*)

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CHAPTER 35

The Modern Cardiac Care Unit

Jonathan P. Piccini, Jason N. Katz, Christopher B. Granger, and L. Kristin Newby

In many ways, the cardiac care unit (CCU) will be a center of convergence for the population and economic trends relating to health care in our society. Our longevity continues to improve steadily and dramatically,[1] but this effect is modest compared with the increase in our functionality.[2] Thus, we have a population that is healthier until the time of acute vascular events, which constitute the leading cause of death and disability by a growing margin. At the same time, societal investment has resulted in an ever-enlarging arsenal of expensive biotechnology: the drug-coated stent,[3] the implantable defibrillator,[4,5] and the left-ventricular assist device[6] are now well entrenched in the clinical arena, and the advent of cell replacement therapy[7] will greatly affect the cost of care and patients' expectations. With more and more recently functional elderly patients making up the bulk of the CCU population and with rapidly advancing technologic capacity, the issue of effectiveness relative to cost and, perhaps more than in younger populations, patient preferences will become dominant in coming years. Clearly, we will not be able to afford to do everything that could prolong life in every patient, nor may that always be an appropriate or even desired goal. Therefore, it will become paramount to develop more systematic approaches to delivering the most effective therapy to patients who will benefit most from it.

The massive increase in heart failure[8] is straining the capacity of CCUs and stimulating discussions of specialized heart-failure units to add to the prevalent chest-pain centers. As left-ventricular assist devices become more widely available, the CCU is likely to become the focus of decision-making for an increasing number of people who are ineligible for cardiac transplantation but who still need to make decisions about treatment that will require enormous expenditures but may significantly lengthen life.

The trends in out-of-hospital outcomes are more difficult to gauge than inpatient trends. We know that out-of-hospital cardiac arrest remains the leading cause of death by far, and we know that extending technology formerly available only in the hospital can significantly reduce mortality and morbidity in communities. Automated external defibrillators, community cardiopulmonary resuscitation (CPR), the performance of electrocardiograms (ECGs) at the scene to identify ST-segment elevation myocardial infarction (STEMI) or high-risk non–ST-segment elevation (NSTE) acute coronary syndromes (ACSs), and techniques for initiating cooling post-cardiac arrest are initial examples of the extension of the CCU into the community. Inadequate effort has been expended to organize these technologies into a comprehensive, evidence-based approach to the application of these emerging therapies. Such an effort will be essential in the next few years.

FROM CORONARY CARE UNIT TO CONTEMPORARY CARDIAC CARE UNIT

Care of the patient with acute myocardial infarction (MI) has changed significantly in the past 50 years. The CCU has been cited as the one of the most important advances in the treatment of acute myocardial infarction, rendering perhaps the largest and longest-lasting impact. The CCU has become such a cornerstone in MI care that it is hard to imagine a time when we did not rely on these specialized intensive care units to care for such highly vulnerable patients. Prior to the development of the CCU in the late 1960s there were few specific interventions available for the care of patients with MI, except for the use of morphine analgesia. The treatment of acute MI was based upon bed rest and "benign neglect."[9] Physicians were powerless in the face of thrombotic, mechanical, and electrical complications for which there were no effective interventions. The development of open-chest and subsequently closed-chest defibrillation, as well as closed-chest massage, provided physicians with the ability to abort life-threatening arrhythmias and circumvent terminal arrest.[10-12]

During a presentation to the British Thoracic Society in 1961, Julian was the first to formally propose the idea of an organized coronary care unit.[13] He proposed that patients with MI should have continuous

electrocardiographic monitoring with an alarm system and that medical staff caring for these patients should be trained in resuscitative efforts. He called for the admission of MI patients to a single location where there were trained nurses who could respond to emergent life-threatening problems without a physician present. In the years to follow, several centers reported their experiences implementing such coronary care units. Killip and Kimball described the care of 250 acute MI patients in a four-bed unit at New York Hospital/Cornell Medical Center. While their work is most often cited for their landmark classification of MI severity, their results suggested that implementation of CCU care reduced in-hospital MI mortality from 27% to 6%. Additionally, their results argued that all patients who experienced cardiac arrest had much higher survival when cared for in the CCU.[14] Similarly, Lown and others at the Peter Bent Brigham Hospital showed that aggressive MI care in the CCU, with an emphasis on arrhythmia suppression, reduced mortality in both the intensive care unit (11.5%) and in-hospital periods (16.9%).[15] The early successes documented with CCUs largely hinged on the central availability of defibrillation and cardiopulmonary resuscitation. The development of mobile resuscitation tools (e.g., crash carts) was an extension of these early efforts to rescue those with cyanotic cardiac arrest. Day was the first to coin the term "code blue" in his description of acute resuscitative care, and he was the first physician to use the term "coronary care unit," in his description of an 11-bed MI unit at Bethany Hospital in Missouri (Fig. 35-1).[16]

The advent of additional technologies that could alter the natural history of acute MI quickly accelerated the evolution of the CCU. The intra-aortic balloon pump, pulmonary artery catheter, and fibrinolytic therapy provided new options for treating and stabilizing ACS patients, but they also simultaneously increased the complexity of the clinical care and the technical services provided by the CCU.[17-19]

As these emerging therapies enabled cardiologists to treat ongoing ischemia and pump failure, they also contributed to the escalating costs associated with improvements in outcomes.[20] The emergence of CCUs across the United States is thought to have been responsible for a 13.5% decline in cardiovascular death between 1968 and 1976.[20,21] However, the high resource use and economic burden characteristic of CCUs has subjected the modern CCU to increasing scrutiny. The financial burdens extend not only to patients and health care systems, but also to payers and society in general. To further illustrate this point, intensive care unit costs increased by more than 200% between 1985 and 2000.[22]

As the CCU has evolved to assume a prominent role in contemporary cardiovascular care, the characteristics of CCU patients also have changed considerably. The prevalence of nonischemic cardiac disorders, and noncardiovascular critical illnesses have increased.[23] CCU patients in today's units are more likely to have multiple comorbid illnesses, which themselves may require intensive care. The reasons behind this escalating comorbidity are many, but certainly include the burgeoning epidemics of obesity, diabetes, heart failure, chronic kidney disease, complications of implantable cardiac devices, and the aging population. Additionally, the expansion of noncardiovascular critical care therapies, including continuous veno-venous hemodialysis, noninvasive ventilation, and therapeutic hypothermia have made the CCU environment all the more complex. The culmination of all of these changes is that the modern CCU is more similar to the medical intensive care unit (ICU) than ever before.

PREHOSPITAL CARE

The extension of the CCU into the prehospital phase involves a shift in thinking from the CCU as a fortress, inside which excellent clinical care can be divorced from the chaos of the external world. Instead, we now know that applying the same principles of evidence, using outcomes studies and clinical trials, can improve the fate of patients in the highest-risk situation—before reaching the hospital—and that we can have a major effect in the period of highest risk in the hospital, the emergency department (ED).

Acute cardiac care begins with the basic principle of encouraging those with symptoms to enter the care system as quickly and efficiently as possible. Most people with symptoms of myocardial ischemia do not seek help quickly, and when they do, most do not call 911 or other emergency medical services (EMS); rather, they arrange nonmedical transport to an emergency facility.[24,25] Though these statements simply present the facts, they belie the underlying complexity of this principle. First, it is based on the assumption that the public understands or can recognize the symptoms of ischemia and the implications of delay. Without those two concepts, people at risk will not enter the system quickly or efficiently. Although the implications of delay may be relatively simple to teach, accurate symptom recognition is difficult even for medically trained personnel, and this has fueled the widespread use of chest pain units. Further, we have limited understanding of what influences even knowledgeable people in the decisions they make when confronted with potential ischemic symptoms. Coupled with wide variability in EMS systems and in patient perceptions of them, fulfilling the basic principle of patients' quick entry into the care system is a great challenge to successful prehospital cardiac care.

The National Heart, Lung, and Blood Institute-sponsored Rapid Early Action for Coronary Treatment (REACT) trial[26] randomized communities to a massive public-relations effort or conventional approaches to attempting to improve responses to symptoms of possible ischemia. The trial showed no effect on time to treatment, appropriate diagnoses, or improved outcomes, but it did show an improvement in the use of EMS as the mode of transport. These results and those of previous studies suggest a need for more-targeted education and refocus of these efforts. Patient delay (prehospital delay) is the major factor in treatment delay, and it has not changed substantially in the reperfusion era.[27,28] Efforts to understand the factors predisposing to delay and to define and target educational efforts to high-risk, high-yield populations may ultimately be a better approach than massive public-education efforts.

In a substudy, the REACT investigators[29] showed that the decision to use EMS depended on the person's thinking about the symptoms: those who lived alone, those who thought that their symptoms were serious enough to take nitroglycerin, and those who were prompted to "go quickly" by others used EMS. Those who called their doctors were less likely to use EMS. Further, communities that had an EMS prepayment plan tended to have greater EMS use than communities in which individuals paid out of pocket (as fee for service) for EMS.

Despite these difficulties, given that the risk of life-threatening arrhythmias and death is greatest in the first few hours after MI,[30] earlier access to life-saving technology is a crucial part of any community cardiac care program. This technology includes the following four main elements: (1) extensions of interventions available in the hospital, for example, the defibrillator; (2) the 12-lead ECG; (3) acute reperfusion therapy; and (4) other drugs.

Time to defibrillation is a critical variable in determining the likelihood of surviving a cardiac arrest. The ultimate approach to this problem is implantation of an automated internal cardioverter/defibrillator (ICD). Even with the expanded Multicenter Automatic Defibrillator Implantation Trial (MADIT)-2 criteria,[4,31] this approach is unlikely to meet

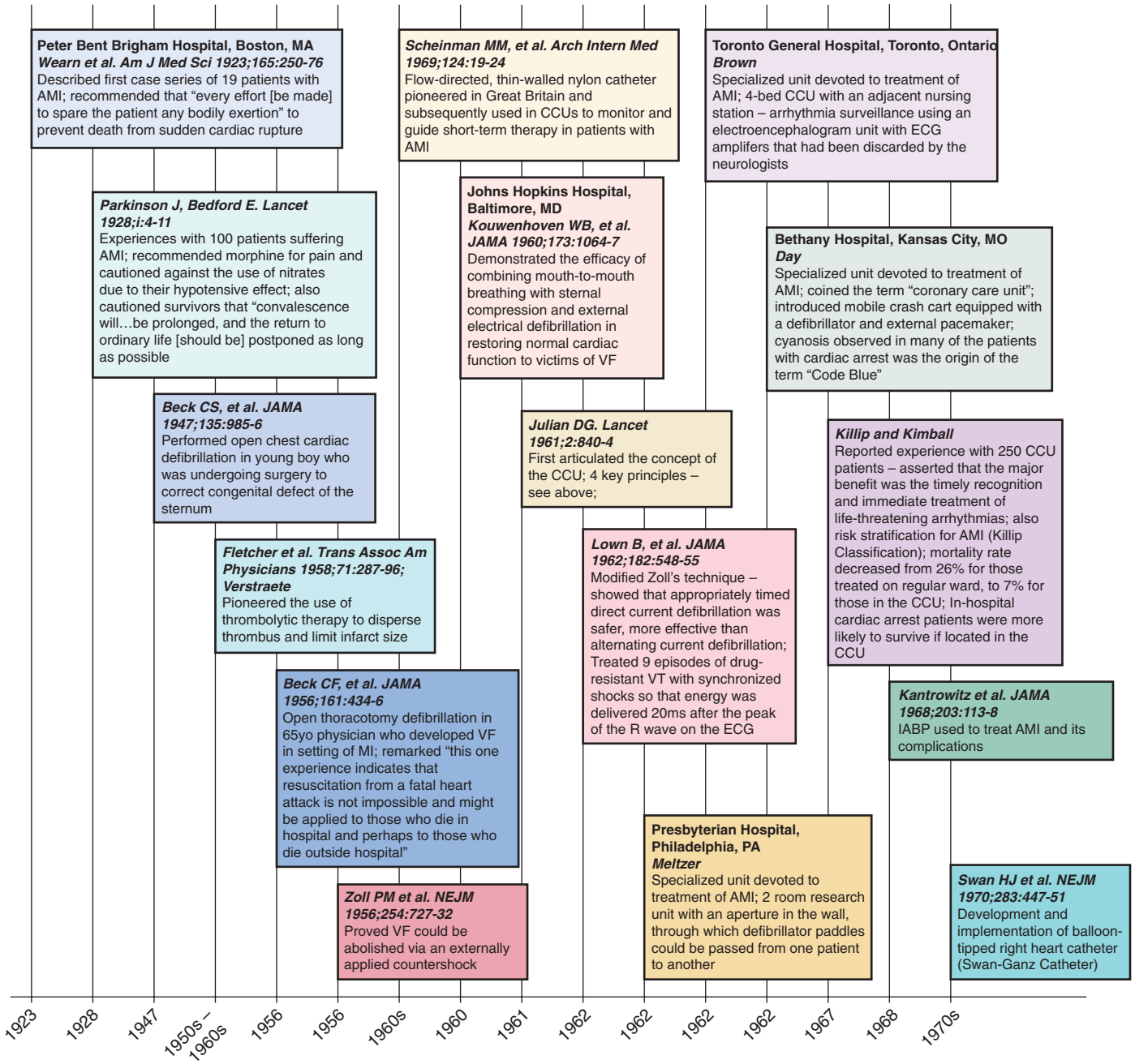

FIGURE 35–1 Milestones in the history of the cardiac care unit. *(Adapted from data in Khush KK, Rapaport E, Waters D: The history of the coronary care unit. Can J Cardiol 2005;21:1041-1045.)*

the need for primary prophylaxis against sudden death because a patient must have already experienced major dysrhythmia or MI to meet these criteria. Another approach is wider distribution of automated external cardioverter defibrillators (AECDs). A recent pilot study from Germany reported a threefold improvement in meaningful recovery from cardiac arrest in the community when AECDs were introduced,[32] and the positive results of deploying AECDs in casinos in Las Vegas have been much discussed.[33]

The standard 12-lead ECG completes the loop for modern acute care of people with thrombosis-induced MI, given that both pathophysiology and definitive therapies have been established for this condition. The standard 12-lead ECG that provides key diagnostic information in patients with ACS symptoms is commonly performed by EMS personnel before hospital arrival. More modern technology can provide wireless ECG transmission from the scene to a handheld liquid crystal display (LCD) to support the on-call cardiologist making triage decisions.[34] A recent study showed that 50% of patients with ECG interpretation of "acute MI" by trained emergency medical technologists and 85% with cardiologist concurrence of "acute MI" will have an acute thrombotic occlusion confirmed during attempted primary percutaneous coronary intervention (PCI).[35] Further, the ability of practicing cardiologists to make both the same ECG diagnosis and the same reperfusion triage decision on paper and on the LCD

of a handheld device has been reported.[36,37] Trials have shown that prehospital transmission of ECGs to cardiologists is associated with a 50-minute reduction in door-to-balloon times.[38,39] Recently, a large registry-based observational study of more than 12,000 patients confirmed that prehospital ECG acquisition is associated with a greater use of reperfusion therapy and improved reperfusion times.[40]

The ST segment has been the portion of the ECG typically used to provide both diagnostic and prognostic information. Ischemia-induced terminal distortion of the QRS complex, however, has been shown to be superior to ST-segment measurements in predicting final acute MI size and assessing the possible effects of fibrinolytic therapy.[41] Also, comparative quantitative changes in T waves and infarction-induced initial distortion of the QRS complex have been shown to add to historical timing in the prediction of limiting MI size through reperfusion therapy.[42]

When the prehospital ECG is perceived to indicate acute coronary thrombosis and the clinical situation is appropriate, early reperfusion therapy can be started intravenously by emergency medical technicians, by rapid administration in the ED, or by PCI in the catheterization laboratory. Electronic transmission of 12-lead ECGs to the hospital ED has been shown to reduce the time to reperfusion via primary PCI by 50 minutes.[38,39,43] The administration of fibrinolytic therapy in the field, also predicated on the availability of 12-lead ECGs at the scene, now has been tested in multiple clinical trials. A systematic overview showed reduced mortality with prehospital versus hospital administration of fibrinolytic therapy,[44] and a pilot trial of field fibrinolysis suggested outcomes comparable with direct PCI.[45] For the most part, field administration of fibrinolytic therapy in the United States has been limited by concerns about liability and the absence of physicians in ambulances. In countries such as France, the system supports the effort, but it is unclear in the United States whether appropriately trained nonphysician personnel can safely give prehospital fibrinolytic or other medical therapy unless there is direct exchange of clinical and ECG information with an on-call physician. When they become available, the results of the ASsessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT)-III Plus study, in which patients from around the world were treated with fibrinolytic therapy in the field by personnel with various clinical backgrounds, should help to address these concerns.

Until reforms in medical liability can be addressed and the safety of prehospital therapy given by nonphysicians is clearly shown and accepted, the first consideration in the United States should be to ensure that all EMS units can capture and transmit in-field 12-lead ECGs. Prehospital services then can focus on timely transfer of patients with acute MI to regional centers capable of rapid administration of fibrinolytic therapy or performance of PCI. For rural areas with long transit times to the nearest hospital, however, improved technology, including electronic transmission of ECGs from the field to on-call physicians, should drive consideration of in-field treatment if qualified nonphysician personnel are available. Development of hybrid, but perhaps safer, alternative approaches to full-dose fibrinolysis also could be an answer. Regardless, in addition to understanding patient-related factors in responding to symptoms and using EMS, broad standardization of EMS services and their improved coordination with regional acute cardiac care facilities will be necessary to enhance prehospital care.

In patients with ACS who are not candidates for acute reperfusion therapy, the amount of depression in the ST segment of the initial ECG has been shown to have value in early risk stratification.[46] Unlike STEMI, it has been difficult to show a dramatic time-dependency of outcome after giving effective therapies in NSTE ACS. Thus, it is difficult to know whether the expense of supplies and training needed for prehospital administration of pharmacologic therapy, other than aspirin and acute therapies such as oxygen, nitrates, and morphine, is warranted. However, having ECG information available from the field should aid in patient triage on arrival and inform decisions for early invasive management strategies. Such information also could improve the likelihood of evidence-based therapies being started early on arrival as well as help identify patients eligible for clinical trials, particularly if integrated with input from on-call cardiology services at the receiving hospital.

Future prehospital cardiac care of patients with ACS may be enhanced by the availability of both practice guidelines and access to the medical literature via handheld devices. Even a simple innovation—such as a new way to provide quantitative information from the 12-lead ECG to the handheld device of the on-call cardiologist—might be useful. A new display of the ECG with all 24 views around "clock faces" surrounding schematic images of the heart, in both the frontal and transverse planes, has been introduced.[47] This might provide added decision support for the cardiologist's interpretation of the initial ECG by indicating the spatial location of the acute ST-segment deviation for more precise localization of the culprit lesion within the coronary artery. A substudy of the Global Use of Strategies To Open occluded coronary arteries (GUSTO) I and II trials has suggested the value of this method.[48]

THE EMERGENCY DEPARTMENT

Although geographically distinct, the ED, and even EDs at separate referral hospitals, must be effectively integrated with the CCU for patients progressing from the outpatient to the critical-care setting. An example of success in a joint ED-cardiology initiative was the Heart Attack Alert Program, which resulted in a 50% reduction in time from ED arrival until fibrinolysis during the 1990s.[49] Because the immediate needs of EDs and CCUs are different and at times even contradictory, regular communication among the two sets of physician and nurse leaders is essential to provide optimal acute cardiac care. Common standards and algorithms should be established (e.g., for reperfusion therapy for acute STEMI). Regular meetings of staff representatives, in which cases are reviewed to highlight problems and successes in integrating emergency and intensive care, constitute one mechanism for continuous improvement.

Hospital-wide ACS protocols should begin in the ED. These protocols should include clear direction on the preferred initial evaluation, the immediate therapeutic approach, and the clinical trials in which the institution is participating. Examples of the ACS protocols at Duke University Medical Center, Durham, N.C., are shown in Figure 35-2. Another important issue for facilities without full cardiac services should be development of a standard approach to determining who should be transferred to a higher-intensity facility and when transfer should occur. In an ideal world, this would be done regionally so that the criteria are standard and the roles and responsibilities of participating facilities (and of the transport links between them and the EMS linking them with the public) are clear. The system would allow such decisions to be made as early as possible after patient arrival in the ED, and with central coordination and input from the EMS and 12-lead ECG in the field, these protocols might be applied even earlier, eliminating the need for transfer to another facility after arrival at the first ED.

Quality measures, as described later, should be viewed jointly by personnel in the ED and the CCU. For example, time to reperfusion therapy could be delayed at multiple points, ranging from obtaining the initial ECG to gaining a

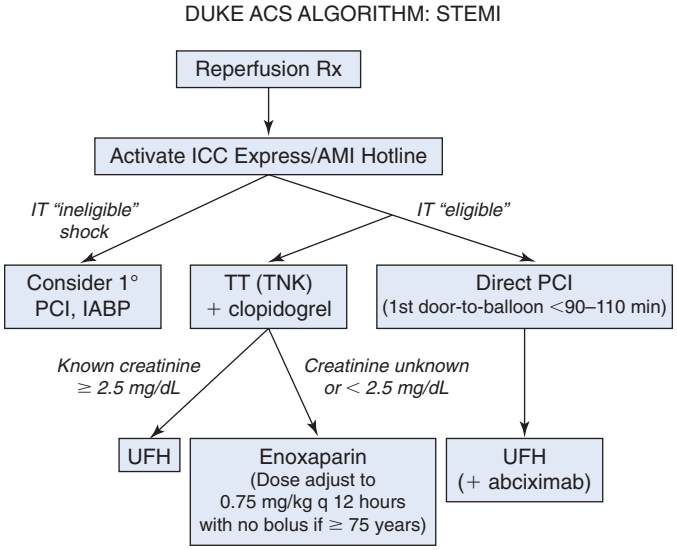

FIGURE 35–2 Algorithm for management of patients with ST-segment elevation MI at Duke University Medical Center, Durham, N.C.

consultation for difficult cases. Ultimately, because time from symptom onset to reperfusion is critical to preservation of myocardium and to patient outcome in STEMI, understanding and eliminating delays at all levels in the system are essential. This can be done only with collaborative review and discussion of the results of quality measures.

PRIMACY OF TIMELY REPERFUSION AND QUALITY IMPROVEMENT

As has been observed in other emergency medical conditions, such as trauma, timely intervention is of paramount importance. In trauma surgery, regional systems of care have been shown to improve response times and outcomes.[50] In the United States, MI deaths outnumber trauma deaths three to one, yet until recently very little attention was paid to systematic, regional approaches to MI care.[51] While CCU care has evolved in the past decade, timely reperfusion in ST-segment elevation ACS remains a prime objective of acute cardiac care. Unfortunately, many patients with acute STEMI do not receive mechanical reperfusion within 90 minutes of their first medical contact. While the reasons for this common failure are multifactorial, they are largely due to system-related barriers.[52] Timely delivery of reperfusion therapy requires collaboration and integration of care beyond the CCU, at outside tertiary care centers, and into the surrounding communities, especially in hospitals without access to primary PCI. In our state, we have successfully implemented a statewide system for reperfusion in STEMI. The Reperfusion of Acute myocardial infarction in North Carolina Emergency departments (RACE) initiative established five regions across the state and involved 65 hospitals and their affiliated EMS (55 non-PCI centers and 10 PCI-capable centers).[53]

The overarching objective of the RACE program was to improve first-medical contact to reperfusion times, via either primary PCI or fibrinolytic therapy. In order to accomplish this goal, the RACE program enacted several key interventions. First, sites were instructed to give authority to the emergency medicine physician on duty to initiate reperfusion, including single-call activation of the cardiac catheterization laboratory. Additional interventions included creation of site-specific reperfusion plans and protocols, local EMS electrocardiogram interpretation training to enable in-the-field diagnosis, and elimination of intravenous drips in order to facilitate rapid interhospital transport. Finally, non-PCI hospitals were encouraged to leave patients on the stretcher, when permissible.

After 19 months, the RACE interventions improved median reperfusion times, including door-to-device from 85 to 74 minutes, $P < .001$; door-to-needle in non-PCI hospitals from 35 to 29 minutes, $P = .0\ 02$; and door-in to door-out from 120 to 71 minutes, $P < .001$, for those transferred to a PCI-capable center. Nonreperfusion rates fell from 23% to 11% in the PCI-capable centers.[53] In one region in central North Carolina, the Duke CCU served as the communication hub for all reperfusion calls from outlying centers. This vertical organizational approach enabled rapid patient care and transport decisions to be enacted after a single phone call.

The RACE approach, which used region-specific tailored approaches to optimal reperfusion was formally adopted by the American Heart Association (AHA) Mission Lifeline initiative.[52] Statewide programs focused on regional delivery of care should undertake future quality initiatives. The CCU, which often serves as the coordinating center and priority receiving center for these patients, must be integrated in these approaches. The RACE experience has shown that the CCU should be actively involved in the reperfusion process, and in so doing can extend its benefit to patients as soon as they come into contact with EMS. Other regional systems, employing a standardized protocol for interhospital STEMI transfer from community hospitals to PCI centers also have shown significant improvements in reperfusion times.[54,55] In addition, the American College of Cardiology (ACC) has launched a quality improvement initiative for reducing door-to-balloon times (D2B: An Alliance for Quality). At the time of this writing, more than 1000 hospitals have joined the D2B effort.[56]

THE CONTEMPORARY CARDIAC CARE UNIT

The contemporary CCU faces the challenge of providing efficient care for patients with complex cardiac conditions using an extensive and complicated set of medical and device options. To succeed, key elements include effective teamwork and communication, systematic approaches, and the use of computer technology to improve performance.

Although major cardiology society guidelines provide a detailed framework for applying evidence-based treatment in a spectrum of patients and situations, their complexity and length—91 pages for the 2002 AHA/ACC STEMI guidelines[57]—essentially preclude their use by physicians in a busy patient-care environment. Guidelines can, however, direct systematic approaches to patient care that can be customized to a hospital or unit, especially when there are information systems to track how care is being provided. For example, a poster outlining a systematic approach to early antithrombotic and interventional care of the spectrum of patients with ACS can be placed in both the ED and the CCU to establish standard approaches that incorporate guidelines and evidence-based approaches. This could include strategies for reperfusion therapy in patients with STEMI, how to use platelet glycoprotein (GP) IIb/IIIa inhibitors, and how to select among anticoagulant options for patients with NSTE ACS. For institutions participating in clinical trials, such a poster also can highlight which patients are eligible for which ongoing trials. In the near future, the goal should be to have such algorithms available to the care team by means of

handheld computers with direct links to the supporting guidelines or literature and to specific dosing guidelines and caveats. Registries such as the Global Registry of Acute Coronary Events (GRACE),[58] and the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry,[40] (which consolidated the efforts of the National Registry of Myocardial Infarction (NRMI),[49] and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines? (CRUSADE),[59] as well as internal quality-assurance data collection, are essential tools in establishing whether treatments are being effectively applied in cardiac emergency and critical care.

After decades of generating negative feelings in the medical community, standardized orders have gained acclaim as part of an effective strategy to reduce medical errors. Standard admission orders can help ensure that common evidence-based treatments, such as aspirin for all patients with ACS, are not forgotten. Standard dosing guidelines for unfractionated heparin, which customize the dose of heparin according to patient weight and call for adjustments according to an algorithm, can improve therapeutic heparin use.[60] Algorithm-driven replacement of potassium and magnesium likewise can allow more accurate and efficient normalization of electrolytes. The ACC-sponsored Guidelines Applied in Practice (GAP) project showed that patients whose doctors were exposed to standard order forms were more likely to be sent home with therapies in alignment with the ACC/AHA guidelines.[61]

CASE MIX AND COMPLEXITY IN THE CARDIAC CARE UNIT

While many are familiar with the landmark study by Killip and Kimball and their classification of hemodynamic severity in acute MI, their seminal observation was the significant survival advantage conferred by CCU care compared with usual medical ward care.[14] Perhaps the single greatest intervention enabled by the CCU was the delivery of timely therapy for life-threatening arrhythmias. Today, these benefits have been extended to the outpatient setting, as multiple clinical trials have demonstrated reductions in arrhythmic and all-cause mortality in patients with significant left ventricular (LV) dysfunction randomized to defibrillator therapy after MI.[62,63] Interestingly, the advent of the ICD has initiated a change in the epidemiology of ventricular tachycardia that has come full circle. Patients who might have otherwise suffered sudden cardiac death outside the hospital, now present to the CCU after isolated episodes of ventricular tachycardia or recalcitrant electrical storm. In our own CCU, the emergence of the ICD in primary prevention settings has led to a significant increase in the number of admissions to the CCU for life-threatening arrhythmias (Fig. 35-3). Patients who present with more than two appropriate ICD discharges in a 24-hour period have electrical storm and represent a particular challenge.[64-66] Such patients have extremely high mortality and often require intense treatment with aggressive beta blockade, sympatholysis, antiarrhythmic drug treatment, and sometimes require intubation and sedation.[67,68] The increasing frequency of ICD admissions has created a need for most CCUs to have 24-hour device interrogation capabilities and access to specialists in electrophysiology.

Further technologic advances in interventional cardiology are also contributing to the escalating acuity and complexity of the CCU population. While not yet mainstream, percutaneous valve replacement, which is reserved for patients who are poor operative candidates, and therefore sicker, will introduce another very complex patient to the CCU environment.

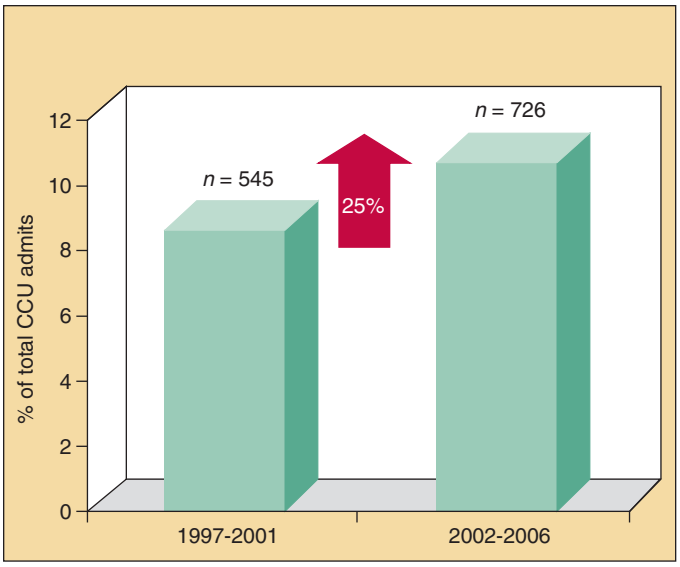

FIGURE 35–3 Increase in admissions for ventricular tachycardia in the CCU at Duke University Medical Center, Durham, N.C. *(From Katz J: Duke University Medical Center, CCU Quality Control Data, 2007.)*

Similarly, the use of percutaneous assist devices, such as the TandemHeart (Cardiac Assist, Inc) and the Impella (Abiomed), will increase the number of bedside devices and technologies that CCU providers will have to be experienced in using and comfortable managing. These devices not only represent a new educational challenge to the multidisciplinary team, but they also enable some patients with extreme comorbidity (who were previously not felt to be candidates for interventional procedures) to proceed with high-risk, high-reward procedures.

COMPLICATIONS

The increasing age of the CCU population and the number and complexity of medical comorbidities among patients admitted to the CCU also create challenges for care delivery that require ever increasing clinical and technical training and competency of the CCU team. As an example, over the past two decades, comorbid admission diagnoses in the Duke CCU have increased significantly. Between 1989 and 2006, the prevalence of septic shock, acute renal failure, and acute respiratory failure have all risen steadily. Accordingly, the median Charlson Comorbidity Index has increased (J.N. Katz, oral personal communication, December 2008), and in turn has been paralleled by escalating resource use, both in the CCU and at discharge. More patients are being discharged to skilled nursing facilities and a greater proportion of patients require advanced outpatient services, such as home health assistance and rehabilitation.

Ventilator-Associated Pneumonia

Patients admitted to the CCU are at risk for iatrogenesis and the multitude of complications associated with critical illness. As a higher percentage of CCU patients require ventilatory support, there will be increasing risk of developing ventilator-associated pneumonia (VAP). Ventilator-associated pneumonia is a costly and potentially life-threatening complication which affects approximately one in five ventilated patients in the CCU.[69] Several measures have been shown to reduce the risk of VAP, including elevation of the head of the

bed to 30 to 45 degrees, gastric ulcer prophylaxis, daily lightening of sedation, and deep venous thrombosis prophylaxis.[70] These measures, often referred to as the "ventilator bundle," should be incorporated into CCU protocols. Incorporation of checklists or protocols of important interventions in critical care have been shown to have an important impact in the ICU setting.[71]

Creatinine Clearance and Dose Adjustment

The incidence of acute renal failure and the prevalence of chronic kidney disease also complicate the care of critically ill cardiovascular patients. Cardiac care unit patients frequently are given medications that are cleared renally. Calculating an estimated creatinine clearance is an essential part of pragmatic CCU clinical care. Two widely used formulas for the estimation of glomerular filtration rates (GFR) are the Cockcroft-Gault formula,[72] and the Modified Diet in Renal Disease (MDRD) formula.[73] In our institution, we base most of our pharmacotherapeutic decisions on the Cockcroft-Gault formula. A review of 46,942 NSTE ACS patients in the CRUSADE registry demonstrated that GFR calculations disagree in up to 20% of patients. These disagreements often lead to significant changes in antithrombotic dosing. Additionally, most of the dosing studies for antithrombotic agents have used the Cockcroft-Gault formula as reflected in the FDA-approved package inserts for these agents. Accordingly, dosing based on the Cockcroft-Gault formula is preferred, particularly in smaller, female, or elderly patients.[74]

ACS-related bleeding is associated with significant morbidity and mortality.[75] Unfortunately, excess dosing of antithrombotic pharmacotherapy has been implicated as an important contributor to bleeding complications after ACS. In addition to patients with renal impairment, older patients, female patients, those with low body weight, diabetes mellitus, and congestive heart failure are also at higher risk of excess antithrombotic dosing.[76] Special attention should be paid to these risk factors and to pharmacotherapeutic dosing in general in the CCU, especially during rounds when treatment plans are prepared. Avoiding bleeding is associated not only with improved patient outcomes but also with significant cost-savings.[77]

Optimizing Outcomes after Cardiac Arrest

Postresuscitation care, including measures to optimize neurologic outcomes, is an essential part of cardiovascular ICU care. Therapeutic hypothermia is an important intervention in patients who remain comatose after cardiac arrest. Among patients in whom spontaneous circulation returns after resuscitation from ventricular fibrillation, cooling to 32° C to 34° C for 12 to 24 hours was associated with significant improvements in neurologic status.[78,79] By using ice packs and an intensive cooling protocol, investigators have shown that cooling can lead to increased likelihood of patient discharge to home (number needed to treat, 4; absolute risk reduction, 23%).[79] Based upon these and other trials, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation has advocated that all unconscious patients with out-of-hospital cardiac arrest should be cooled to 32° C to 34° C for 12 to 24 hours when the presenting rhythm is ventricular fibrillation.[80] While not yet proven, therapeutic hypothermia is also likely to be beneficial in victims of other methods of cardiac arrest, including in-hospital arrest.

THE TEAM APPROACH

Strong physician leadership of a CCU is essential so that medical decisions, reflecting consensus, can be applied systematically to ensure the highest-quality care. In many practice situations, because physicians who admit patients to the CCU may belong to competing practice groups, systematic application of standards of care is possible only if there is a mechanism (preferably a unit medical director) to adjudicate differences. For day-to-day care, some units may have one attending physician responsible for the care of all patients admitted to the unit, a situation better suited to central decision-making, whereas others may have separate physicians responsible for each patient with no formal alignment of providers. Given the growing complexity of acute cardiac care, the ever-increasing arsenal of expensive biotechnology and pharmacologic treatment options, and the increasing demands on the CCU and its physicians to make decisions regarding their use, the latter situation is no longer tenable in most modern CCUs.

In addition to focusing delivery of such care in highly specialized centers, only cardiologists experienced with substantial volumes and spectra of critically ill patients should care directly for cardiology patients in ICUs. At centers that do not provide these services, protocols defining the appropriate transfer of patients should be developed in conjunction with referral centers. In addition, modern CCU physicians should be expected to meet high standards for clinical competency and compliance with practice guidelines. Widespread implementation of such a change in the model will require the skills of a strong physician-leader able to traverse the political minefield inherent in such an approach, which ultimately has the best interests of patient care as its focus. Outside interests may drive such organization as well. The Leapfrog group, which represents a coalition of organizations that pay for health care in the United States, has made the presence of full-time intensivists and computerized physician order entry criteria of quality for referral of patients by the employers who constitute this group.[81]

When attending physicians are not immediately available in person, they should have a fax machine or Internet access to ECGs (and, ideally, coronary angiography and echocardiogram data) for immediate interpretation at home or office, or this responsibility should be delegated to someone physically present. In addition to competence in standard invasive intensive-care unit procedures, physicians staffing CCUs should be able to perform and interpret echocardiograms. Training in advanced cardiac life support is also advisable.

Nursing

Competent and compassionate nurses are the most important team members of the successful CCU. After accounting for the fixed costs of facilities, more than 80% of the direct CCU budget can be attributed to nursing personnel. The complexity of the CCU calls for a team of specially trained, relatively independent practitioners. In our environment, the CCU nurse is the defender of the standard of care. Given that physicians spend limited time in the CCU, it is the nurse who identifies when variations in prescribing or procedure use are reasonable and when they deviate from the standard of care. The nurse is the gatekeeper for the patient, ensuring that the right thing is being done at the right time. Timely and effective communication between nurses and physician-leaders in real time is critical to avoiding conflict when differences of opinion arise.

Because the demand for CCU beds varies uncontrollably, it is critical to develop and maintain standards for flexibility in staffing. This can be done by maintaining a core of "budgeted" nurses based on analysis of occupancy and severity-of-illness trends. Shifts in the patient census then can be handled by cross-training with other cardiology units so that nurses can move to and from those areas when needed,

maintaining a flexible workforce that can be tapped when overflow occurs and allowing judicious filling of empty beds with selected non-CCU patients. Each unit must develop a specific solution, but common to all approaches is the need for intensive, standards-based education of nurses.

In a large CCU, in addition to the usual nurse management and educator system, a nurse-clinician focused on family and physician communication has been and remains a critical feature. The nurse-clinician plays an essential role in maintaining quality data regarding performance improvement and in being the liaison between the families and the health care team. In many cases, miscommunications among the patient, family, nurses, and doctors can be avoided or resolved with external oversight from an experienced nurse-clinician. The compelling results from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT)[82] caused us to conclude that significant resources must be put toward the end of life as well as improving longevity. Experience in our CCU has shown that end-of-life preferences and decisions are often influenced by race, cultural norms, and spirituality (R.W. Johnson, oral personal communication, December 2008). Experienced nurse-clinicians are often instrumental in helping families articulate end-of-life preferences, cope with illness, and provide emotional support. The nurse-clinician is critical in developing and maintaining a multidisciplinary protocol for the withdrawal of life support and the initiation of end-of-life care.

Pharmacist Role

The clinical pharmacist is an essential partner in the CCU. The publicity about patient harm from medication errors has emphasized the importance of expert review and advice regarding use of drugs. Using the definition of medical errors put forward by the Institute of Medicine—having the wrong plan or making an error in the execution of the correct plan[83]—few patients make it through a CCU experience without at least one medical error. Given the age of this population and the high prevalence of comorbidity, including variable renal and hepatic function, CCU patients are particularly at risk for bleeding, arrhythmias, and other adverse effects.

Pharmacy support should address three areas: education of physicians and nurses as to safe use of common medications and their combinations; establishment of systems to guide effective and safe use of drugs; and personal review of medication use in patients in the CCU. As electronic pharmacy, laboratory, and medical-order systems become more sophisticated, algorithms programmed into the system can flag potential problems. Recent studies have shown that dosing errors in administration of fibrinolytic therapy can result in catastrophic patient outcomes,[84] which might be avoided with built-in electronic checks and feedback to the physician about dosing before drug administration. Appropriate dosing is critical in the care of patients with ACS. Data from the CRUSADE registry has demonstrated that hospitals with safe-dosing practices are more likely to apply evidence-based therapies. Not surprisingly, excessive dosing of antithrombotic therapies is more common in vulnerable populations and is associated with increased bleeding complications.[76,85] One area of extreme importance is dose adjustment for renally excreted drugs. In recent research done by the Centers for Education and Research on Therapeutics, the dose of dofetilide was correctly given in fewer than 40% of patients.[86] Integrated electronic systems in both the CCU and the cardiology ward could substantially reduce these types of prescribing errors. Until such systems are widely available, however, pharmacist oversight of prescribing for the individual patient's clinical situation and changes in condition remains essential.

Effective sedation of the agitated patient is a special challenge in the intensive-care setting. This can be addressed by including pharmacist input into developing a systematic approach for this population. Further, as the use of invasive procedures, mechanical prostheses, and ventilators in the CCU continues to escalate, antibiotics are becoming ubiquitous, but cardiologists have difficulty staying abreast of the latest information about antibiotic prescribing and overuse; this leads to significant risk of resistant organisms in the local environment. We think that a clinically knowledgeable pharmacist should review drug orders on all CCU patients at least daily and that special attention should be paid to renally excreted drugs, sedation, and antibiotics.

Other Team Members

Ideally, members of the entire care team participate in the discussion and design of the care plan. Respiratory technicians play an important role in optimizing ventilator management, and physical and occupational therapists can ensure early and consistent rehabilitation. Maintaining adequate nutritional support, balancing increased metabolic demands against possible renal or hepatic impairment, is essential to the recovery of the critically ill patient. Recovering patients with ACS and their families are most available for and attuned to education about dietary modification and its role in long-term management of coronary disease and heart failure in the CCU.

The importance of "hotel functions" in a system of cardiac care cannot be underestimated. Maintenance of facilities and supplies and efficient cleaning and turnover of rooms are critical. Additionally, the unscheduled nature of CCU admissions calls for extensive communication efforts within and between hospitals. In the United States, the criteria for transfer and admission seem to vary as a function of whether the unit is full.[87] Given the growing epidemic of vascular disease in the aging, it seems unlikely that facilities will be built at the same pace as the demand. This inevitable fact underscores the need for a regional system to ensure that patients are not caught between hospitals or transferred inappropriately when beds may be empty at different hospitals.

Communication with the Family

Similar to the need for a pediatrician to communicate with the parents of a sick child, the CCU physicians and staff must effectively communicate with and support the families of their critically ill patients. More liberal, flexible visiting hours tend to be most supportive of families. A particularly important time for intensive support and counseling of families is at the end of life, including situations in which life support is withdrawn from a patient with a terminal and irreversible illness. A nurse with interest and expertise in critical care and in family communication and support can be an invaluable part of the care team when extensive family interactions are needed. A related need, for less acutely ill patients, is patient and family teaching. A patient in the early days of recovery after an acute MI, for example, is a captive and generally receptive audience for teaching about smoking cessation, diet, lifestyle changes, and what to expect from upcoming procedures. A patient-education booklet customized to the institution is an important adjunct for patient education.

Assessment of Quality

Understanding the quality of medical care has been potentiated by focus from various organizations, most notably the Institute of Medicine. Its two seminal reports—To Err Is Human[83] and Crossing the Quality Chasm[88]—lay out an

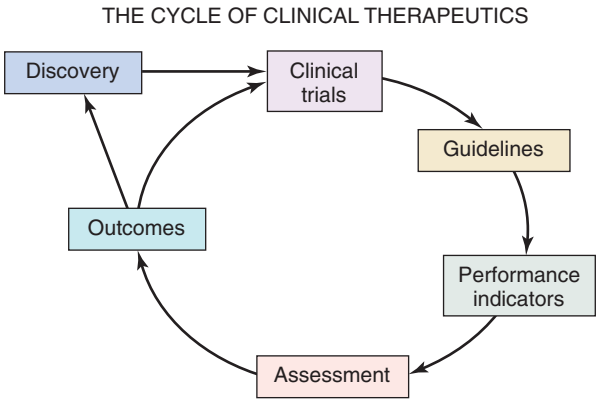

FIGURE 35–4 Model for the integration of quality into the therapeutic development cycle. *(From Califf RM, Peterson ED, Gibbons RJ, et al: Integrating quality into the cycle of therapeutic development. J Am Coll Cardiol 2002;40:1895-1901.)*

BOX 35-1 Joint Committee Core Performance Measures for Myocardial Infarction[91]

1. Aspirin given at arrival
2. Aspirin prescribed at discharge
3. Patients with left-ventricular ejection fraction <40% prescribed an ACE inhibitor at discharge
4. Adult smoking cessation advice/counseling
5. Beta blocker prescribed at discharge
6. Beta blocker given at arrival
7. Time from arrival to start of fibrinolysis
8. Time from arrival to start of primary percutaneous coronary intervention
9. Inpatient mortality

approach to providing quality health care that is forming the basis for research in and measurement of quality.

A broad approach in cardiovascular medicine,[89] into which the CCU readily fits, has been to attempt to develop a cycle of quality (Fig 35-4). Given an excellent idea based on a plausible biologic construct, multiple studies are needed before a definitive phase III or phase IV trial can be performed. If this trial or series of trials is of adequate quality, the results can be used to create a clinical practice guideline. Particular trials of adequate power, done in a relevant environment with modern background therapy and producing a robust result, can result in a class I (proven to be effective), level of evidence A (based on multiple trials or a mega trial) or B (based on less definitive trials) recommendation. Definitive clinical practice guideline recommendations can be translated into performance indicators that measure whether a practitioner, practice, hospital, or system is adhering to guideline standards, and aggregates of performance indicators can be used to characterize clinical performance.

The CCU is an ideal environment in which to test approaches to the cycle of quality and an important place to develop constructs that work because of the massive public health implications. In fact, many of the standards of care that currently exist are based on clinical trials in acute cardiac care.

Members of the care provider team should meet regularly to address optimizing care of the CCU patient. In 2004, The Joint Commission (JC) and the Centers for Medicare and Medicaid Services (CMS) agreed to common quality measures for acute MI care. In doing so, the JC's ORYX Core Measures and CMS quality measures became the standard by which ACS care will be measured at the provider and hospital level. These measures include rapid reperfusion with either fibrinolysis or primary angioplasty; the use of aspirin at arrival and discharge, beta blockers at discharge, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers for LV dysfunction; and smoking cessation counseling.[90]

Rapid use of cardioversion/defibrillation for pulseless ventricular arrhythmias also should be ensured. One of the most important functions of a CCU is highly effective intervention for treatable life-threatening cardiac arrhythmias. In fact, the concept of the CCU was originally established in large part for that capability.[91] For each minute of delay in defibrillation, there is an approximate 10% decrease in survival[92,93]; thus, every CCU should establish the goal of treating every instance of ventricular fibrillation with defibrillation within 1 minute of its occurrence. To do so, the unit must establish a system for responding to ventricular fibrillation and must measure the time from onset of ventricular fibrillation until first defibrillator shock to ensure that the goal is accomplished. Box 35-1 lists a set of performance indicators for MI adopted by the JC.[90] Our goal is to exceed the criteria for adherence to guidelines by a wide margin.

For NSTE ACS, Peterson and colleagues have shown a broad variance in adherence to the ACC/AHA guidelines.[94] Importantly, the hospitals that most closely adhered to guideline recommendations had the lowest mortality rates.[94] Whether these better outcomes result directly from the therapies studied or represent a marker of the ability to organize complex therapeutic schemes among multiple practitioners remains to be discovered.

Our approach to quality measurement in the CCU has been to use existing registries to produce measures of adherence to performance indicators. Previously, in the ST-elevation setting, we participated in the National Registry for Myocardial Infarction (NRMI),[49] and in the NSTE ACS setting we participated in the CRUSADE registry.[59] Beginning in 2007, these registries were merged to form the ACTION Registry—Get With The Guidelines (ACTION Registry—GWTG, which is organized by the AHA and the National Cardiovascular Data Registry (NCDR). The ACTION Registry—GWTG uses Internet-based data entry and provides sites with comparative quarterly outcomes. These quarterly reports allow institutions to identify areas for quality care improvement. In addition to participating in national registries, at Duke we conduct a monthly morbidity and mortality conference to review issues of coordination of care and communication. When a major incident occurs with a patient, consideration is given to a sentinel event analysis in conjunction with the hospital's quality system. An ultimate measure of quality for the CCU of the future would be the morbidity and mortality rates for the community. Such a measure obviously would require collaboration between the CCU and EMS.

THE CARDIAC CARE UNIT AS A RESEARCH PLATFORM

The evolution of the modern cardiac care unit has allowed clinicians to treat patients with increasingly complex cardiovascular maladies. Along with advancing critical illness and greater comorbidities among today's CCU patients, technologic discoveries and improved models of health care delivery have made these specialized units integral parts of contemporary health systems. At the same time, this evolution has created a truly fertile environment from which to conduct novel clinical research. Not only are we now able to

study large populations of patients with acute coronary syndromes and severely decompensated heart failure, but we can now also hope to better examine such concepts as circulatory support for refractory cardiogenic shock, sepsis-induced myocardial dysfunction, mechanical ventilation and sedation in cardiac illness, and the influence of organ failure on ischemic outcomes. The potential for platforms of research in the modern CCU is seemingly limitless, the results of which should lead to improvements in patient care by standardizing cardiac critical care delivery, developing more effective operational models, creating physician decision-support tools, and improving clinician and staff training.

Using the CCU as a platform for effective research will depend upon successful multicenter and multidisciplinary collaborations as well as the successful integration of clinical care and research teams and data and IT support infrastructures. This may include developing uniform databases for data abstraction, organizing robust research networks with viable resources for implementing novel research constructs, and it will heavily depend upon our ability to secure significant contributions from academic, government, industrial and philanthropic resources. Potential areas of CCU-based research include economic analyses of cardiovascular critical care delivery, genomic studies of critical care susceptibility among cardiac patients, telemedicine and electronic medical information, the effects of multidisciplinary clinical integration, novel education and training practices, and end-of-life issues.

FINANCES

The CCU is a major cost center for hospitals, but it also serves as a source of patient throughput that generates substantial revenue. Major percutaneous intervention and cardiac surgical programs are not sustainable without adequate CCU support. Thus, the efficient management of CCU services, personnel, and supplies plays a major role in the financial stability of hospitals. Because the CCU is integrated with other cardiovascular services, it is critical to view financial reports for cardiac services as a whole, rather than simply evaluating the CCU as a "tub on its own bottom."

Most costs in the CCU are attributable to facilities, equipment, and personnel. Management of facilities and equipment requires a sophisticated understanding of fixed and variable costs and an ability to estimate the effect on clinical outcomes and other costs of having or not having these components. For example, given a fixed investment in CCU beds, the rapid availability of cardiac-intervention facilities becomes a major determinant of whether the beds will be filled to spread the fixed costs adequately. Management of nursing personnel has been discussed, but the quality of care may depend more on this factor than any other. A recent study showed that 30-day mortality increases by 7% with each additional patient per nurse, at the same time increasing the risk of nurse "burnout" by 23% and the odds of job dissatisfaction by 15%.[95] Thus, the nurse-manager and CCU director must work incessantly to ensure that adequate nurses are staffed for first-rate patient care while maintaining fiscal responsibility.

Ultimately, given the likelihood of progressive dissociation between what is possible and the costs of effective therapy, the fate of the CCU will depend on how well its leaders can make the case for incremental spending for more benefit. This advocacy will be more effective if the CCU can set the standard within the hospital for efficient resource use. We think that participation in the research enterprise is a critical component of identifying which approaches provide enough benefit to justify the cost and which should be eschewed.[96]

CONCLUSIONS

The CCU is an increasingly complex entity, and it must be integrated into a broad community and hospital approach to preventing and treating cardiovascular disease. A focus on standards of care, with derivative rational allocation of costs to provide the greatest benefit, will enable the CCU of the future to do more good for more people. To meet this demand, the CCU must be led by physicians and nurses with a broad view of clinical medicine, finance, and management.

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