The AHA Guidelines and Scientific Statements Handbook

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Edited by Valentin Fuster
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Edited by

Valentin Fuster
Mount Sinai School of Medicine
One Gustave Levy Place
Box 1030
New York
USA

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Contents

Contributors vii

Preface x

1 Chronic Stable Angina 1
Theodore D. Fraker, Stephan D. Fihn, and Raymond J. Gibbons

2 Unstable Angina/Non-ST-Elevation Myocardial Infarction 25
Jeffrey L. Anderson and Nanette Kass Wenger

3 ST-Elevation Myocardial Infarction 46
Elliott M. Antman

4 Cardiac Rehabilitation and Secondary Prevention Programs 91
Mark A. Williams and Gary J. Balady

5 Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease 108
Sidney C. Smith, Jr.

6 Percutaneous Coronary Intervention 117
Sidney C. Smith, Jr.

7 Coronary Artery Bypass Graft Surgery 134
Cullen D. Morris, Kim Eagle, Robert A. O'Rourke, and Robert A. Guyton

8 Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery 152
Lee A. Fleisher

9 Lower Extremity Peripheral Artery Disease 165
Alan T. Hirsch and Ziv J. Haskal

10 Cholesterol Management in the Context of Risk Factor Profile 187
Scott M. Grundy

11 Hypertension 196
Clive Rosendorff

12 Cardiovascular Disease Prevention in Women 214
Kathy Berra and Nanette Kass Wenger

13 Heart Failure 223
Sharon A. Hunt and Mariell Jessup

14 Cardiomyopathies 236
Barry J. Maron

15 Atrial Fibrillation 244
Valentin Fuster and Lars Rydén

16 Supraventricular Arrhythmias 255
Carina Blomström-Lundqvist and Melvin Scheinman

17 Ventricular Arrhythmias and Sudden Cardiac Death 270
A. John Camm and Douglas P. Zipes

18 Valvular Heart Disease 293
Robert O. Bonow

19 Infective Endocarditis 312
Larry M. Baddour, Kathryn A. Taubert, Michael H. Gewitz, and Walter R. Wilson

20 Cardiac CT Imaging 336
Matthew J. Budoff and Allen J. Taylor

Appendix Update on Coronary Artery Bypass Surgery: Current and Future Trends 347
Robert A. O'Rourke

Other Statements Published in 2008 353

Index 355

COI Table 373

List of Contributors

Jeffrey L. Anderson, MD, FACC, FAHA
Association Chief of Cardiology
Cardiology Department
LDS Hospital
8th Avenue C Street
Salt Lake City, UT 84143-0001, USA

Elliott M. Antman, MD, FAHA
Professor of Medicine
Harvard Medical School
Director, CCU
Cardiovascular Division
Brigham and Women's Hospital
Senior Investigator
TIMI Study Group
75 Francis Street
Boston, MA 02115-6106, USA

Larry M. Baddour, MD
Professor of Medicine
Mayo Clinic
200 1st. Street SW
Rochester, MN 55905-0002, USA

Gary J. Balady, MD, FAHA
Director, Non Invasive Cardiac Labs
Director, Preventive Cardiology
Boston Medical Center
Professor of Medicine
Boston University School of Medicine
883 East Newton Street
Boston, MA 02118-2308, USA

Kathy Berra, MSN, ANP, FAAN, FAHA
Stanford Prevention Research Center
Stanford University Medical School
Hoover Pavilion, Room N229
211 Quarry Road N241
Stanford, CA 94305-5705, USA

Carina Blomström-Lundqvist, MD
Department of Cardiology
Uppsala University Hospital
S-751 85 Uppsala
Sweden

Robert O. Bonow, MD, MACC, FAHA
Goldberg Distinguished Professor
Northwestern University Feinberg School of Medicine
Chief, Division of Cardiology
Co-Director, Bluhm Cardiovascular Institute
Northwestern Memorial Hospital
201 East Huron Street, Suite 10-240
Chicago, IL 60611-2996, USA

Matthew J. Budoff, MD, FAHA, FACC
Association Professor of Medicine
Division of Cardiology
Los Angeles Biomedical Research Institute at Harbor-UCLA
1124 West Carson Street, RB2
Torrance, CA 90502-2006, USA

John Camm, MD
Professor of Clinical Cardiology
Division of Cardiac and Vascular Sciences
St. George's University of London
Cranmer Terrace
London, SW17 0RE
United Kingdom

Kim A. Eagle, MD, FACC
Albion Walter Hewlett Professor of Internal Medicine
Chief of Clinical Cardiology
Director, Cardiovascular Center
University of Michigan Cardiovascular Center
1500 East Medical Drive, Suite 2131
Ann Arbor, MI 48109-5852, USA

Stephan D. Fihn, MD, MPH, FACP
Chief Quality and Performance Officer
Department of Veterans Affairs
1100 Olive Way STE 1400
Seattle, WA 98101-3801, USA

Lee A. Fleisher, MD, FACC, FAHA
Robert Dunning Dripps Professor and Chair
Department of Anesthesiology and Critical Care
Professor of Medicine
University of Pennsylvania School of Medicine
3400 Spruce Street, Suite 680 Dulles
Philadelphia, PA 19104, USA

Theodore D. Fraker, Jr., MD, FACC
Professor of Clinical Medicine
Associate Division Director for Clinical Affairs and Operations
Division of Cardiology, Department of Medicine
The Ohio State University College of Medicine
248 Davis Heart & Lung Research Institute, 473 West 12th Avenue
Columbus, OH 43210, USA

Valentin Fuster, MD, PhD, FAHA
Mount Sinai School of Medicine
One Gustave Levy Place
Box 1030
New York, NY, USA

Michael H. Gewitz, MD, FAHA
Physician-in-Chief/Executive Director
Maria Fareri Children's Hospital at Westchester Medical Center
Professor and Vice Chair, Pediatrics
Chief, Pediatric Cardiology
New York Medical College
Valhalla, NY 10595, USA

Raymond J. Gibbons, MD, FAHA
Professor of Medicine
Mayo Clinic Fnd.- Gonda
200 1st Street SW
Rochester, MN 55905-0001, USA

Scott M. Grundy, MD, PhD, FAHA
Director, Center for Human Nutrition
UT Southwestern Medical Center
Department of Clinical Nutrition
5323 Harry Hines Building
Dallas, TX 75390-7200, USA

Robert A. Guyton, MD
Professor and Chief, Division of Cardiothoracic Surgery
Department of Surgery
Emory University School of Medicine
1365 Clifton Road NE
Atlanta, GA 30322-1013, USA

Ziv J. Haskal, MD, FAHA, FSIR, FACR
Professor and Vice Chair, Radiology
Chief, Division of Interventional Radiology
University of Maryland School of Medicine
22 E Greene Street
Baltimore, MD 21201, USA

Alan T. Hirsch, MD
Division of Epidemiology and Community Health
School of Public Health
University of Minnesota
1300 South 2nd Street, Suite 300
Minneapolis, MN 55454, USA

Sharon A. Hunt, MD, FACC, FAHA
Professor, Division of Cardiovascular Medicine
Stanford University
300 Pasteur Drive, Falk CVRB
Palo Alto, CA 94305, USA

Mariell Jessup MD, FAHA, FACC
Professor of Medicine
University of Pennsylvania School of Medicine
Heart Failure/Transplant Program
3400 Spruce Street
Philadelphia, PA 19104, USA

Barry J. Maron, MD, FACC
Director, Hypertrophic Cardiomyopathy Center
Minneapolis Heart Institute Foundation
920 East 28th. Street, Suite 620
Minneapolis, MN 55407-1157, USA

Cullen D. Morris, MD
Assistant Professor of Surgery (Cardiothoracic)
The Emory Clinic, Inc.
Medical Director of Cardiothoracic Surgery
Athens Regional Medical Center
1270 Prince Ave., Suite 303
Athens, GA 30606, USA

Robert A. O'Rourke, MD, MACP, MACC, FAHA
Professor of Medicine Emeritus
University of Texas Health Science Center
116 Village Circle
San Antonio, TX 78232-2827, USA

Clive Rosendorff, MD, PhD, DScMed, FAHA
Mount Sinai School of Medicine
and the James J. Peters VA Medical Center
130 West Kingsbridge Road
Bronx, NY 10468-3904, USA

Lars Rydén, MD, FRCP, FESC
Department of Cardiology
Karolinska University Hospital
171 76 Stockholm
Sweden

Melvin Scheinman, MD
University of California, San Francisco
500 Parnassus Avenue
San Francisco, CA 94143-2203, USA

Sidney C. Smith, Jr., MD, FAHA
Professor of Medicine
University of North Carolina at Chapel Hill
Center for Cardiovascular Science and Medicine
CB # 7075, 6th Floor Burnett Womack Building
99 Manning Drive
Chapel Hill, NC 27599-7075, USA

Kathryn A. Taubert, PhD, FAHA
Adjunct Professor, U Texas Southwestern Medical School
Senior Scientist, American Heart Association
AHA National Center
7272 Greenville Avenue
Dallas, TX 75231, USA

Allen J. Taylor, MD, FAHA
Chief, Cardiology Service, Professor of Medicine
Walter Reed Army Medical Center
6900 Georgia Avenue, NW
Building 2, Room 4A34
Washington, DC 20307-5001, USA

Nanette Kass Wenger, MD, FAHA
Professor of Medicine (Cardiology)
Emory University School of Medicine
Chief of Cardiology
Grady Memorial Hospital
Consultant, Emory Heart and Vascular Center
49 Jesse Hill Jr. Drive, SE
Atlanta, GA 30303, USA

Mark A. Williams, PhD, FACSM, FAACVPR
Director, CVD Prevention and Rehabilitation
Cardiac Center of Creighton University
3006 Webster Street
Omaha, NE 68131-2027, USA

Walter R. Wilson, MD
Professor of Medicine
Mayo Clinic
200 1st Street SW
Rochester, MN 55905-0002, USA

Douglas P. Zipes, MD, FAHA
Distinguished Professor
Indiana University School of Medicine
Krannert Institute of Cardiology, Suite E315
1800 North Capitol Avenue
Indianapolis, IN 46202, USA

Preface

The American Heart Association (AHA) has produced science consistently for over 75 years. And for over 25 years, based on the best scientific medical evidence, the AHA has produced guidelines with the American College of Cardiology Foundation, as well as scientific statements, with a direct interest in ensuring that all patients receive a good quality standard of cardiovascular care. Thus, the AHA is constantly looking for ways to improve adherence to guidelines by caregivers since heart disease, stroke, and other cardiovascular diseases remain the No. 1 killer in the United States and a leading cause of permanent disability worldwide [1].

Although adherence to guidelines should improve patient care and outcomes, many studies have shown that the standard of care as defined by guidelines and statements does not sufficiently reach patients [2–4]. Accordingly, our objective is to try to enhance education of caregivers through this simple and user-friendly, summarized and updated "The AHA Guidelines and Scientific Statements Handbook" so that they may easily adhere to it and find it useful to improve patient care and outcomes. Most of the recent AHA guidelines and statements are summarized and presented here, all in one text. We have also asked authors to provide a "future directions" section on each chapter, to expand upon recent trials and research that might affect guidelines in the future. When appropriate, a brief comparison to other guidelines (usually from the European Society of Cardiology) is also provided, indicated in purple text. Furthermore, also refer to the website for this book, www.Wiley.com/go/AHAGuidelineHandbook, as it will be sequentially updated with the latest statements and guideline news as well as providing succinct and helpful bibliographies.

In terms of format, the ACC/AHA Task Force on Practice Guidelines have established schema for classification of recommendations and level of evidence. This schema is summarized in the table on the facing page, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect. In trying to mimic the significance of the green, yellow and red lights that guide the circulation of the vehicles, "The AHA Guidelines and Scientific Statements Handbook" also uses similar colors in its recommendations. Thus, Class I or "must do" recommendations are titled in green text; Class IIa and IIb or respectively "it is appropriate" and "it is not inappropriate" recommendations are titled in yellow text; and Class III or "must not do" recommendations are titled in red. Also, within the context of a user-friendly and practical format, searching at the index, for example, for the word "angina," automatically will guide you to the various guidelines and statements that deal with "angina."

I cannot conclude this brief introduction without expressing my sincere thanks to all of the authors of the parent committees who, with their time and effort, contributed to the original guidelines and statements; and, of course, I am particularly grateful to the authors of the handbook, who all served on the parent committees and very generously contributed to this project by meeting a very tight schedule. I warmly thank my collaborators at the American Heart Association and Wiley-Blackwell for meeting once a week in a conference call at 5.30 am, and I am particularly grateful to Ms Heather Goodell, Ms Kate Newell and Mr Oliver Walter. Finally, I would like to express my deepest appreciation to the American Heart Association for giving me the opportunity to serve as Editor of this first edition of "The AHA Guidelines and Scientific Statements Handbook". Hopefully, this is the beginning of a useful educational tool for the healthcare community and, most importantly, for the promotion of cardiovascular health in our patients.

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Valentin Fuster, MD, PhD
Past President American Heart Association
Past President World Heart Federation
Director Mount Sinai Heart Center,
New York, NY

Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

1 Chronic Stable Angina

Theodore D. Fraker, Stephan D. Fihn, and Raymond J. Gibbons

Introduction
Classification of angina pectoris
Demographics of angina pectoris
Patients with new onset or changing anginal symptoms
The development of practice guidelines
Asymptomatic individuals
Recommendations for the management of patients with chronic stable angina
Diagnosis
A. History and physical examination
B. Associated conditions
C. Noninvasive testing
D. Invasive testing: value of coronary angiography
Risk stratification
A. Clinical evaluation
B. Noninvasive testing
C. Use of exercise test results in patient management
D. Coronary angiography and left ventriculography
Treatment
A. Pharmacologic therapy
Coronary disease risk factors and evidence that treatment can reduce the risk for coronary disease events
Patient follow-up: monitoring of symptoms and antianginal therapy
Future issues
Special consideration for women
New information on percutaneous revascularization to be considered for the next chronic stable angina guideline
New therapeutic agents to be considered for the next chronic stable angina guideline

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Introduction

Angina pectoris is a clinical syndrome characterized by discomfort in the chest, jaw, back or arm typically aggravated by exertion or emotional stress and relieved by rest or nitroglycerin. Angina pectoris is usually associated with epicardial coronary artery disease including one or more obstructions of greater than 70%, but it can also occur in patients with valvular heart disease, hypertrophic cardiomyopathy, or uncontrolled hypertension. Symptoms are thought to result from regional or global myocardial ischemia due to mismatch between myocardial oxygen supply and demand (Table 1.1). In women, angina pectoris can be seen in the absence of obvious epicardial coronary artery obstruction or other cardiac pathology, presumably due to coronary artery endothelial dysfunction or other factors. Chronic stable angina refers to anginal symptoms that occur daily, weekly or less frequently and are typically predictable and reproducible [1–4].

Classification of angina pectoris

Chest discomfort can be described as typical angina, atypical angina or non-anginal chest pain, depending upon whether or not symptoms occur with increased myocardial oxygen demand and are relieved by rest or nitroglycerin. Typical angina is usually described as a sensation of chest tightness, heaviness, pressure, burning or squeezing sometimes accompanied by radiation to the inner arm, jaw, back or epigastrium. What makes the discomfort "typical" is the predictable relationship to increased activity (implying increased myocardial

Table 1.1 Conditions provoking or exacerbating ischemia

Increased oxygen demand	Decreased oxygen supply
Noncardiac	*Noncardiac*
Hyperthermia	Anemia
Hyperthyroidism	Hypoxemia
Sympathomimetic toxicity (e.g., cocaine use)	Pneumonia
Hypertension	Asthma
Anxiety	Chronic obstructive pulmonary disease
Arteriovenous fistulae	Pulmonary hypertension
	Interstitial pulmonary fibrosis
Cardiac	Obstructive sleep apnea
Hypertrophic cardiomyopathy	Sickle cell disease
Aortic stenosis	Sympathomimetic toxicity (e.g., cocaine use)
Dilated cardiomyopathy	Hyperviscosity
Tachycardia	Polycythemia
Ventricular	Leukemia
Supraventricular	Thrombocytosis
	Hypergammaglobulinemia
	Cardiac
	Aortic stenosis
	Hypertrophic cardiomyopathy

oxygen consumption) and subsequent relief with rest or NTG (Table 1.2).

The severity of angina pectoris is customarily described using the Canadian Cardiovascular Society Classification System (Table 1.3).

Table 1.2 Clinical classification of chest pain

Typical angina (definite)
(1) Substernal chest discomfort with a characteristic quality and duration that is (2) provoked by exertion or emotional stress and (3) relieved by rest or NTG.

Atypical angina (probable)
Meets two of the above characteristics.

Noncardiac chest pain
Meets one or none of the typical anginal characteristics.

Modified from Diamond, IACC, 1983.

Demographics of angina pectoris

Coronary artery disease, the principal cause of angina pectoris, is thought to be present in 13,200,000 American adults, about half of whom (6,500,000 or 3.8% of the population) have angina pectoris or chest pain [4]. The incidence of stable angina is about 400,000 persons per year and there are an estimated 63,000 hospital discharges per year (2003) [4]. The annual mortality rate is hard to assess in the US since angina pectoris is rarely listed on death certificates as the cause of death. Data from the European Society of Cardiology estimates the annual mortality rate ranges from 0.9–1.4 % and the annual incidence of non-fatal MI ranges from 0.5–2.6% [3]. Only about 20% of cardiac events are preceded by long-standing angina [4].

Table 1.3 Grading of angina pectoris by the Canadian Cardiovascular Society Classification System

Class I
Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid or prolonged exertion at work or recreation.

Class II
Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.

Class III
Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions at a normal pace.

Class IV
Inability to carry on any physical activity without discomfort – anginal symptoms may be present at rest.

Source: Campeau L. Grading of angina pectoris [letter]. Circulation, 1976;54:522–523. Copyright © 1976. American Heart Association. Inc. Reprinted with permission.

Patients with new onset or changing anginal symptoms

Patients who present with a history of angina that has recently started or has changed in frequency, severity or pattern are often classified as having unstable angina. These patients can be subdivided by their short-term risk of death (Table 1.4). Patients at high or moderate risk often have an acute coronary syndrome caused by coronary artery plaques that have ruptured. Their risk of death is intermediate, between that of patients with acute MI and patients with stable angina. The initial evaluation of high- or moderate-risk patients with unstable angina is best carried out in the inpatient setting. However, low-risk patients with unstable angina have a short-term risk similar to that of patients with stable angina. Their evaluation can be accomplished safely and expeditiously in an outpatient setting. The recommendations made in these guidelines do not apply to patients with high- or moderate-risk unstable angina but are applicable to the low-risk unstable angina group.

The development of practice guidelines

The American College of Cardiology/American Heart Association Task Force on Practice Guidelines met in 2001 and 2002 to update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina. This guideline was published in 2003. In 2007, a subgroup of the writing committee updated the 2002 Chronic Stable Guideline to be consistent with the AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease. In 2006, the European Society of Cardiology [3] published its own guideline which differs somewhat from the ACC/AHA guideline. Both sets of guidelines will be considered in this chapter.

The Classification of Recommendations (COR) and Level of Evidence (LOE) are expressed in the ACC/AHA/ESC format (see table in front of book). These recommendations are evidence-based from published data where applicable.

Asymptomatic individuals

This chapter and the recommendations that follow are intended to apply to symptomatic patients. These were the focus of the original 1999 guideline. The 2002 update included additional sections and recommendations for asymptomatic patients with known or suspected coronary artery disease (CAD). Such individuals are often identified on the basis of evidence of a previous myocardial infarction by history and/or electrocardiographic changes, coronary angiography, or an abnormal noninvasive test, including coronary calcification on computed tomography (CT). Multiple ACC/AHA guidelines, scientific statements and expert consensus documents have discouraged the use of noninvasive tests, including ambulatory monitoring, treadmill testing, stress echocardiography, stress myocardial perfu-

Table 1.4 Short-term risk of death or nonfatal myocardial infarction in patients with unstable angina

High risk	Intermediate risk	Low risk
At least one of the following features must be present:	No high-risk features but must have any of the following:	No high- or intermediate-risk feature but may have any of the following:
Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD	Increased angina frequency, severity, or duration
Pulmonary edema, most likely related to ischemia	Rest angina (>20 min or relieved with sublingual nitroglycerin)	Angina provoked at a lower threshold
Angina at rest with dynamic ST changes ≥1 mm	Nocturnal angina	New onset angina with onset 2 weeks to 2 months prior to presentation
Angina with new or worsening MR murmur	Angina with dynamic T-ware changes	Normal or unchanged ECG
Angina with S_3 or new/worsening rales	New onset CCSC III or IV angina in the past 2 weeks with moderate or high likelihood of CAD	
Angina with hypotension	Pathologic Q waves or resting ST depression ≤1 mm in multiple lead groups (anterior, inferior, lateral)	
	Age >65 years	

CCSC indicates Canadian Cardiovascular Society Classification.

Note: Estimation of the short-term risks of death and nonfatal MI in unstable angina is a complex multivariable problem that cannot be fully specified in a table such as this. Therefore, the table is meant to offer general guidance and illustration rather than rigid algorithms.

sion, and CT, in asymptomatic individuals. Their inclusion in the 2002 guideline did not represent an endorsement of such tests for the purposes of screening, but rather an acknowledgment of the clinical reality that asymptomatic patients may present for further evaluation after abnormal tests. In general, the recommendations that appeared in the 2002 update for asymptomatic individuals were qualitatively similar to those that appear here for symptomatic patients. In some cases, either the class of the recommendation or the level of evidence, or both, were lower for asymptomatic patients. Interested readers may consult the 2002 guideline update on either the ACC or AHA website (www.americanheart.org or www.acc.org).

Recommendations for the management of patients with chronic stable angina

Note: Recommendations in **black** are from the ACC/AHA guideline and recommendations in **purple** are from the European Society of Cardiology guideline.

Diagnosis

A. History and physical examination

Recommendation

Class I

In patients presenting with chest pain, a detailed symptom history, focused physical examination, and directed risk-factor assessment should be performed. With this information, the clinician should estimate the probability of significant CAD (i.e., low (i.e., ≤5%), intermediate (>5% and <90%), or high [≥90%]) (Tables 1.5 and 1.6). *(Level of Evidence: B)*

B. Associated conditions

Recommendations for initial laboratory tests for diagnosis

Class I

1 Hemoglobin. *(Level of Evidence: C)*

2 Fasting glucose. *(Level of Evidence: C; B)*

3 Fasting lipid panel, including total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and calculated low-density lipoprotein (LDL) cholesterol. *(Level of Evidence: C; B)*

Table 1.5 Pretest likelihood of CAD in symptomatic patients according to age and sex* (combined Diamond/Forrester and CASS Data)

	Nonanginal Chest pain		Atypical angina		Typical angina	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

*Each value represents the percent with significant CAD on catheterization.

Table 1.6 Comparing pretest likelihoods of CAD in low-risk symptomatic patients with high-risk symptomatic patients – Duke Database

	Nonanginal Chest pain		Atypical angina		Typical angina	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
35 y	3–35	1–19	8–59	2–39	30–88	10–78
45 y	9–47	2–22	21–70	5–43	51–92	20–79
55 y	23–59	4–25	45–79	10–47	80–95	38–82
65 y	49–69	9–29	71–86	20–51	93–97	56–84

Each value represents the percent with significant CAD. The first is the percentage for a low-risk, mid-decade patient without diabetes, smoking, or hyperlipidemia. The second is that of the same age patient with diabetes, smoking, and hypelipidemia. Both high- and low-risk patients have normal resting ECGs. If ST-T-wave changes or Q waves had been present, the likelihood of CAD would be higher in each entry of the table.

4 Full blood count including Hb and white cell count *(Level of Evidence: B)*
5 Creatinine *(Level of Evidence: C)*
6 Markers of myocardial damage if evaluation suggests clinical instability or acute coronary syndrome *(Level of Evidence: A)*
7 Thyroid function if clinically indicated *(Level of Evidence: C)*

Class IIa
Oral glucose tolerance test *(Level of Evidence: B)*

Class IIb
1 Hs C-reactive protein *(Level of Evidence: B)*
2 Lipoprotein a, ApoA, and ApoB *(Level of Evidence: B)*
3 Homocysteine *(Level of Evidence: B)*
4 HbA1c *(Level of Evidence: B)*
5 NT-BNP *(Level of Evidence: B)*

C. Noninvasive testing

1. ECG/chest X-ray: Recommendations for electrocardiography, chest X-ray, or electron-beam computed tomography in the diagnosis of chronic stable angina

Class I
1 A rest ECG in patients without an obvious noncardiac cause of chest pain is recommended. *(Level of Evidence: B)*
2 A rest ECG during an episode of chest pain is recommended. *(Level of Evidence: B)*
3 A chest X-ray in patients with signs or symptoms of congestive heart failure (CHF), valvular heart disease, pericardial disease, or aortic dissection/aneurysm is recommended. *(Level of Evidence: B)*
4 A resting ECG is recommended while the patient is pain-free. *(Level of Evidence: C)*

Class IIa

A chest X-ray in patients with signs or symptoms of pulmonary disease is reasonable. *(Level of Evidence: B)*

Class IIb

1 A chest X-ray in other patients may be considered. *(Level of Evidence: C)*

2 Electron-beam computed tomography may be considered. *(Level of Evidence: B)*

3 A routine periodic ECG in the absence of clinical change may be considered. *(Level of Evidence: C)*

2. Recommendations for diagnosis of obstructive CAD with exercise ECG testing without an imaging modality

Class I

Exercise ECG is recommended in patients with an intermediate pretest probability of CAD (>5% and <90%) based on age, gender, and symptoms, including those with complete right bundle-branch block or less than 1 mm of ST depression at rest (exceptions are listed below in classes II and III). *(Level of Evidence: B)* (See Tables 1.5 and 1.6).

Class IIa

Exercise ECG is reasonable in patients with suspected vasospastic angina. *(Level of Evidence: C)*

Class IIb

1 Exercise ECG may be considered in patients with a high pretest probability of CAD by age, gender, and symptoms. *(Level of Evidence: B)*

2 Exercise ECG may be considered in patients with a low pretest probability of CAD by age, gender, and symptoms. *(Level of Evidence: B)*

3 Exercise ECG may be considered in patients taking digoxin whose ECG has less than 1 mm of baseline ST-segment depression. *(Level of Evidence: B)*

4 Exercise ECG may be considered in patients with ECG criteria for LVH and less than 1 mm of baseline ST-segment depression. *(Level of Evidence: B)*

5 Routine periodic exercise ECG may be reasonable in the absence of clinical change. *(Level of Evidence: C)*

Class III

1 Exercise ECG is not recommended in patients with the following baseline ECG abnormalities.

a. Pre-excitation (Wolff–Parkinson–White) syndrome. *(Level of Evidence: B)*

b. Electronically paced ventricular rhythm. *(Level of Evidence: B)*

c. More than 1 mm of ST depression at rest. *(Level of Evidence: B)*

d. Complete left bundle-branch block. *(Level of Evidence: B)*

2 Exercise ECG is not recommended in patients with an established diagnosis of CAD owing to prior MI or coronary angiography; however, testing can assess functional capacity and prognosis, as discussed in Section III. *(Level of Evidence: B)*

3. Echocardiography: Recommendations for echocardiography for diagnosis of cause of chest pain in patients with suspected chronic stable angina pectoris

Class I

1 Echocardiography is recommended for patients with systolic murmur suggestive of aortic stenosis or hypertrophic cardiomyopathy *(Level of Evidence: C, B)*

2 Echocardiography is recommended for evaluation of extent (severity) of ischemia (e.g., LV segmental wall-motion abnormality) when the echocardiogram can be obtained during pain or within 30 min after its abatement. *(Level of Evidence: C)*

3 Echocardiography is recommended for patients with suspected heart failure *(Level of Evidence: B).*

4 Echocardiography is recommended for patients with prior MI *(Level of Evidence: B).*

5 Echocardiography is recommended for patients with LBBB, Q waves or other significant pathological changes on ECG, including electrocardiographic left anterior hemiblock *(Level of Evidence: C).*

Class IIb

Echocardiography may be considered in patients with a click or murmur to diagnose mitral valve prolapse [15]. *(Level of Evidence: C)*

Table 1.7 Comparative advantages of stress echocardiography and stress radionuclide perfusion imaging in diagnosis of CAD

Advantages of stress echocardiography

1. Higher specificity
2. Versatility – more extensive evaluation of cardiac anatomy and function
3. Greater convenience/efficacy/availability
4. Lower cost

Advantages of stress perfusion imaging

1. Higher technical success rate
2. Higher sensitivity – especially for single vessel coronary disease involving the left circumflex
3. Better accuracy in evaluating possible ischemia when multiple resting IV wall motion abnormalities are present
4. More extensive published database – especially in evaluation of prognosis

Class III

Echocardiography is not recommended in patients with a normal ECG, no history of MI, and no signs or symptoms suggestive of heart failure, valvular heart disease, or hypertrophic cardiomyopathy. *(Level of Evidence: C)*

4. Stress imaging studies: echocardiographic and nuclear recommendations for cardiac stress imaging as the initial test for diagnosis in patients with chronic stable angina who are able to exercise

See Table 1.7.

Class I

1 Exercise myocardial perfusion imaging or exercise echocardiography is recommended in patients with an intermediate pretest probability of CAD who have one of the following baseline ECG abnormalities:

a. Pre-excitation (Wolff–Parkinson–White) syndrome. *(Level of Evidence: B)*

b. More than 1 mm of ST depression at rest. *(Level of Evidence: B)*

2 Exercise myocardial perfusion imaging or exercise echocardiography is recommended in patients with prior revascularization (either PCI or CABG). *(Level of Evidence: B)*

3 Adenosine or dipyridamole myocardial perfusion imaging is recommended in patients with an intermediate pretest probability of CAD and one of the following baseline ECG abnormalities:

a. Electronically paced ventricular rhythm. *(Level of Evidence: C)*

b. Left bundle-branch block. *(Level of Evidence: B)*

4 Exercise myocardial perfusion imaging or exercise echocardiography is recommended in patients with a non-conclusive exercise ECG but reasonable exercise tolerance, who do not have a high probability of significant coronary disease and in whom the diagnosis is still in doubt. *(Level of Evidence: B)*

Class IIa

Exercise myocardial perfusion imaging or exercise echocardiography is reasonable in the following circumstances:

1 Patients with prior revascularization (PCI or CABG) in whom localization of ischaemia is important. *(Level of evidence: B)*

2 As an alternative to exercise ECG in patients where facilities, costs, and personnel resources allow. *(Level of evidence: B)*

3 As an alternative to exercise ECG in patients with a low pre-test probability of disease such as women with atypical chest pain. *(Level of Evidence: B)*

4 To assess functional severity of intermediate lesions on coronary arteriography. *(Level of Evidence: C)*

5 To localize ischaemia when planning revascularization options in patients who have already had arteriography. *(Level of Evidence: B)*

6 Pharmacological stress imaging techniques [either echocardiography or perfusion] are reasonable with the same Class I indications outlined above, where local facilities favor pharmacologic rather than exercise stress. *(Level of Evidence: B)*

Class IIb

1 Exercise myocardial perfusion imaging or exercise echocardiography may be considered in patients with a low or high probability of CAD who have one of the following baseline ECG abnormalities:

a. Pre-excitation (Wolff–Parkinson–White) syndrome. *(Level of Evidence: B)*

b. More than 1 mm of ST depression. *(Level of Evidence: B)*

2 Adenosine or dipyridamole myocardial perfusion imaging may be considered in patients with a low or high probability of CAD and one of the following baseline ECG abnormalities:

a. Electronically paced ventricular rhythm. *(Level of Evidence: C)*

b. Left bundle-branch block. *(Level of Evidence: B)*

3 Exercise myocardial perfusion imaging or exercise echocardiography may be considered in patients with an intermediate probability of CAD who have one of the following:

a. Digoxin use with less than 1 mm ST depression on the baseline ECG. *(Level of Evidence: B)*

b. LVH with less than 1 mm ST depression on the baseline ECG. *(Level of Evidence: B)*

4 Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography may be considered as the initial stress test in a patient with a normal rest ECG who is not taking digoxin. *(Level of Evidence: B)*

5 Exercise or dobutamine echocardiography may be considered in patients with left bundle-branch block. *(Level of Evidence: C)*

5. Recommendations for cardiac stress imaging as the initial test for diagnosis in patients with chronic stable angina who are unable to exercise

(Pharmacological stress with imaging techniques [either echocardiography or perfusion] is recommended in the initial assessment of angina with the same Class I, IIa and IIb indications outlined above, if the patient is unable to exercise adequately.)

Class I

1 Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography is recommended in patients with an intermediate pretest probability of CAD. *(Level of Evidence: B)*

2 Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography is recommended in patients with prior revascularization (either PCI or CABG). *(Level of Evidence: B)*

Class IIb

1 Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography may be considered in patients with a low or high probability of CAD in the absence of electronically paced ventricular rhythm or left bundle-branch block. *(Level of Evidence: B)*

2 Adenosine or dipyridamole myocardial perfusion imaging may be considered in patients with a low or a high probability of CAD and one of the following baseline ECG abnormalities:

a. Electronically paced ventricular rhythm. *(Level of Evidence: C)*

b. Left bundle-branch block. *(Level of Evidence: B)*

3 Dobutamine echocardiography in patients with left bundle-branch block. *(Level of Evidence: C)*

6. Recommendations for ambulatory ECG for initial diagnostic assessment of angina

Class I

An ambulatory ECG is recommended for angina with suspected arrhythmia. *(Level of Evidence: B)*

Class IIa

An ambulatory ECG may be reasonable for suspected vasospastic angina. *(Level of Evidence: C)*

7. Recommendations for the use of CT angiography in stable angina

Class IIb

CT angiography may be considered in patients with a low pre-test probability of disease, with a nonconclusive exercise ECG or stress imaging test. *(Level of Evidence: C)*

D. Invasive testing: value of coronary angiography

Recommendations for coronary angiography to establish a diagnosis in patients with suspected angina, including those with known CAD who have a significant change in anginal symptoms

Class I

1 Coronary angiography is recommended in patients with known or possible angina pectoris who have survived sudden cardiac death. *(Level of Evidence: B)*

2 Coronary angiography is recommended in patients with severe stable angina (Class 3 or greater of Canadian Cardiovascular Society Classification, with a high pre-test probability of disease, particularly if the symptoms are inadequately responding to medical treatment.) *(Level of Evidence: B)*
3 Coronary angiography is recommended in patients with serious ventricular arrhythmias. *(Level of Evidence: C)*
4 Coronary angiography is recommended in patients previously treated by myocardial revascularization (PCI, CABG), who develop early recurrence of moderate or severe angina pectoris. *(Level of Evidence: C)*

Class IIa

1 Coronary angiography is reasonable in patients with an uncertain diagnosis after noninvasive testing in whom the benefit of a more certain diagnosis outweighs the risk and cost of coronary angiography. *(Level of Evidence: C)*
2 Coronary angiography is reasonable in patients who cannot undergo noninvasive testing because of disability, illness, or morbid obesity. *(Level of Evidence: C)*
3 Coronary angiography is reasonable in patients with an occupational requirement for a definitive diagnosis. *(Level of Evidence: C)*
4 Coronary angiography is reasonable in patients who by virtue of young age at onset of symptoms, noninvasive imaging, or other clinical parameters are suspected of having a nonatherosclerotic cause for myocardial ischemia (coronary artery anomaly, Kawasaki disease, primary coronary artery dissection, radiation-induced vasculopathy). *(Level of Evidence: C)*
5 Coronary angiography is reasonable in patients in whom coronary artery spasm is suspected and provocative testing may be necessary. *(Level of Evidence: C)*
6 Coronary angiography is reasonable in patients with a high pretest probability of left main or three-vessel CAD. *(Level of Evidence: C)*
7 Coronary angiography is reasonable in patients with a high risk of restenosis after PCI, if PCI has been performed in a prognostically important site. *(Level of Evidence: C)*

Class IIb

1 Coronary angiography may be considered in patients with recurrent hospitalization for chest pain in whom a definite diagnosis is judged necessary. *(Level of Evidence: C)*
2 Coronary angiography may be considered in patients with an overriding desire for a definitive diagnosis and a greater-than-low probability of CAD. *(Level of Evidence: C)*

Class III

1 Coronary angiography is not recommended in patients with significant comorbidity in whom the risk of coronary arteriography outweighs the benefit of the procedure. *(Level of Evidence: C)*
2 Coronary angiography is not recommended in patients with an overriding personal desire for a definitive diagnosis and a low probability of CAD. *(Level of Evidence: C)*

Risk stratification

The recommendations that follow are for risk stratification by clinical evaluation, including ECG and laboratory tests, in stable angina.

A. Clinical evaluation

Class I

1 A detailed clinical history and physical examination is recommended including BMI and/or waist circumference in all patients, also including a full description of symptoms, quantification of functional impairment, past medical history, and cardiovascular risk profile. *(Level of Evidence: B)* (Figure 1.1).
2 Resting ECG in all patients is recommended. *(Level of Evidence: B)*

B. Noninvasive testing

Recommendations for measurement of rest LV function by echocardiography or radionuclide angiography in patients with chronic stable angina

Class I

1 Echocardiography or RNA is recommended in patients with a history of prior MI, pathologic Q waves, or symptoms or signs suggestive of heart

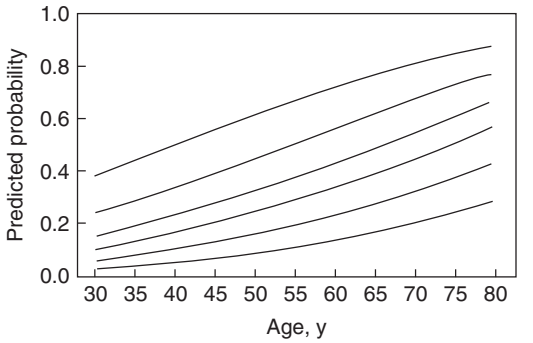

Fig. 1.1 Nomogram showing the probability of severe (three-vessel or left main) coronary disease based on a five-point score. One point is awarded for each of the following variables: male gender, typical angina, history and electrocardiographic evidence of myocardial infarction, diabetes and use of insulin. Each curve shows the probability of severe coronary disease as a function of age. From Hubbard *et al.* with permission.

failure to assess LV function. *(Level of Evidence: B)*

2 Echocardiography is recommended in patients with a systolic murmur that suggests mitral regurgitation to assess its severity and etiology. *(Level of Evidence: C)*

3 Echocardiography or RNA is recommended in patients with complex ventricular arrhythmias to assess LV function. *(Level of Evidence: B)*

4 Resting echocardiography is recommended in patients with hypertension. *(Level of Evidence: B)*

5 Resting echocardiography is recommended in patients with diabetes. *(Level of Evidence: C)*

Class IIa

Resting echocardiography is recommended in patients with a normal resting ECG without prior MI who are not otherwise to be considered for coronary arteriography. *(Level of Evidence: C)*

Class III

1 Echocardiography or RNA is not recommended for routine periodic reassessment of stable patients for whom no new change in therapy is contemplated. *(Level of Evidence: C)*

2 Echocardiography or RNA is not recommended in patients with a normal ECG, no history of MI, and no symptoms or signs suggestive of CHF. *(Level of Evidence: B)*

Recommendations for exercise testing risk assessment and prognosis in patients with an intermediate or high probability of CAD

Class I

1 Exercise testing is recommended in patients undergoing initial evaluation. (Exceptions are listed below in Classes IIb and III) *(Level of Evidence: B)*

2 Exercise testing is recommended in patients after a significant change in cardiac symptoms. *(Level of Evidence: C)*. (Tables 1.8, 1.9 and 1.10).

Class IIa

Exercise testing is reasonable in patients post-revascularization with a significant deterioration in symptomatic status. *(Level of Evidence: B)*

Class IIb

1 Exercise testing may be considered in patients with the following ECG abnormalities:

a. Pre-excitation (Wolff-Parkinson-White) syndrome. *(Level of Evidence: B)*

b. Electronically paced ventricular rhythm. *(Level of Evidence: B)*

c. More than 1 mm of ST depression at rest. *(Level of Evidence: B)*

d. Complete left bundle-branch block. *(Level of Evidence: B)*

2 Exercise testing may be considered in patients who have undergone cardiac catheterization to identify ischemia in the distribution of coronary lesion of borderline severity. *(Level of Evidence: C)*

3 Exercise testing may be considered in post-revascularization patients who have a significant change in anginal pattern suggestive of ischemia. *(Level of Evidence: C)*

Class III

Exercise testing is not recommended in patients with severe comorbidity likely to limit life expectancy or prevent revascularization. *(Level of Evidence: C)*

Table 1.8 Survival according to risk groups based on Duke Treadmill Scores

Risk group (score)	Percentage of total	Four-year survival	Annual mortality (percent)
Low (≥+5)	62	0.99	0.25
Moderate (–10 to +4)	34	0.95	1.25
High (<–10)	4	0.79	5.0

The Duke treadmill score equals the exercise time in minutes minus (5 times the ST-segment deviation, during or after exercise, in millimeters).

Table 1.9 Noninvasive risk stratification

High-risk (greater than 3% annual mortality rate)

1. Severe resting left ventricular dysfunction (LVEF < 35%)
2. High-risk treadmill score (score ≤–11)
3. Severe exercise left ventricular dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate-risk (1–3% annual mortality rate)

1. Mild/moderate resting left ventricular dysfunction (LVEF = 35% to 49%)
2. Intermediate-risk treadmill score (–11 < score < 5)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

Low-risk (less than 1% annual mortality rate)

1. Low-risk treadmill score (score ≥5)
2. Normal or small myocardial perfusion defect at rest or with stress*
3. 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%).

C. Use of exercise test results in patient management

Recommendation for exercise testing in patients with chest pain 6 months or more after revascularization

Class IIb

Exercise testing may be considered in patients with a significant change in anginal pattern suggestive of ischemia. *(Level of Evidence: B)*

Recommendations for cardiac stress imaging as the initial test for risk stratification of patients with chronic stable angina who are able to exercise

Class I

1 Exercise myocardial perfusion imaging or exercise echocardiography is recommended to identify the extent, severity, and location of ischemia in patients who do not have left bundle-branch block or an electronically paced ventricular rhythm and

Table 1.10 CAD Prognostic Index

Extent of CAD	Prognostic weight (0–100)	5-Year survival rate (%)*
1-vessel disease, 75%	23	93
>1-vessel disease, 50% to 74%	23	93
1-vessel disease, ≥95%	32	91
2-vessel disease	37	88
2-vessel disease, both ≥95%	42	86
1-vessel disease, ≥95% proximal LAD	48	83
2-vessel disease, ≥95% LAD	48	83
2-vessel disease, ≥95% proximal LAD	56	79
3-vessel disease	56	79
3-vessel disease, ≥95% m at least 1	63	73
3-vessel disease, 75% proximal LAD	67	67
3-vessel disease, ≥95% proximal LAD	74	59

*Assuming medical treatment only. CAD indicates coronary artery disease; LAD, left anterior descending artery. From Califf RM, Armstrong PW. Carver JR, *et al*: Task Force 5. Stratification of patients into high-, medium- and low-risk subgroups for purposes of risk factor management. J Am Coll Cardiol. 1996;27:964–1047.

who either have an abnormal rest ECG or are using digoxin. *(Level of Evidence: B)*

2 Dipyridamole or adenosine myocardial perfusion imaging is recommended in patients with left bundle-branch block or electronically paced ventricular rhythm. *(Level of Evidence: B)*

3 Exercise myocardial perfusion imaging or exercise echocardiography is recommended to assess the functional significance of coronary lesions (if not already known) in planning PCI. *(Level of Evidence: B)*

4 Exercise myocardial perfusion imaging or exercise echocardiography is recommended in patients with a non-conclusive exercise ECG, but intermediate or high probability of disease. *(Level of Evidence: B)*

Class IIa

1 Exercise myocardial perfusion imaging or exercise echocardiography is reasonable in patients with a deterioration in symptoms post-revascularization. *(Level of Evidence B)*

2 Exercise myocardial perfusion imaging or exercise echocardiography is reasonable as an alternative to exercise ECG in patients, in which facilities, cost, and personnel resources allow. *(Level of Evidence: B)*

3 Pharmacological stress imaging techniques [either echocardiography or perfusion] are reasonable with the same Class I indications outlined above, where local facilities favor pharmacologic rather than exercise stress *(Level of Evidence: B)*

Class IIb

1 Exercise or dobutamine echocardiography may be considered in patients with left bundle-branch block. *(Level of Evidence: C)*

2 Exercise, dipyridamole, or adenosine myocardial perfusion imaging, or exercise or dobutamine echocardiography may be considered as the initial test in patients who have a normal rest ECG and who are not taking digoxin. *(Level of Evidence: B)*

Class III

1 Exercise myocardial perfusion imaging is not recommended in patients with left bundle-branch block. *(Level of Evidence: C)*

2 Exercise, dipyridamole, or adenosine myocardial perfusion imaging, or exercise or dobutamine echocardiography is not recommended in patients with severe comorbidity likely to limit life expectation or prevent revascularization. *(Level of Evidence: C)*

Recommendations for cardiac stress imaging as the initial test for risk stratification of patients with chronic stable angina who are unable to exercise

Class I

1 Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography is recommended to identify the extent, severity, and location of ischemia in patients who do not have left bundle-branch block or electronically paced ventricular rhythm. *(Level of Evidence: B)*

2 Dipyridamole or adenosine myocardial perfusion imaging is recommended in patients with left bundle-branch block or electronically paced ventricular rhythm. *(Level of Evidence: B)*

3 Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography is recommended to assess the functional significance of coronary lesions (if not already known) in planning PCI. *(Level of Evidence: B)*

Class IIb

Dobutamine echocardiography may be considered in patients with left bundle-branch block. *(Level of Evidence: C)*

Class III

Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography is not recommended in patients with severe comorbidity likely to limit life expectation or prevent revascularization. *(Level of Evidence: C)*

D. Coronary angiography and left ventriculography

Recommendations for coronary angiography for risk stratification in patients with chronic stable angina

See Figure 1.2.

Class I

1 Coronary angiography is recommended in patients with disabling (Canadian Cardiovascular Society [CCS] classes III and IV) chronic stable angina despite medical therapy. *(Level of Evidence: B)* (Table 1.11).

2 Coronary angiography is recommended in patients with high-risk criteria on noninvasive testing (Table 1.10) regardless of anginal severity. *(Level of Evidence: B)* (Table 1.11).

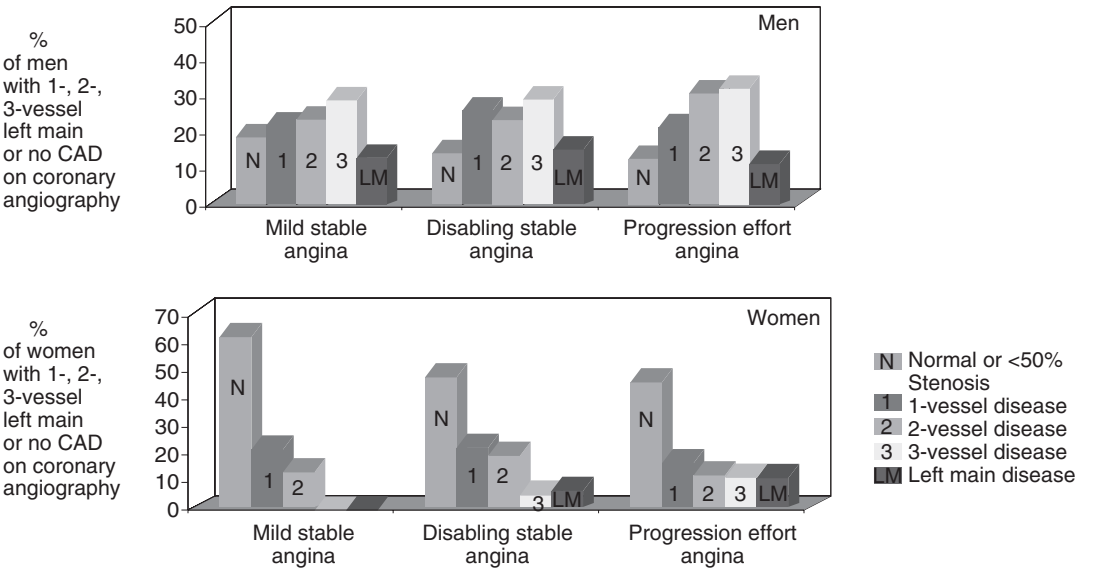

Fig. 1.2 Coronary angiography findings in patients with chronic effort-induced angina pectoris. Top: Percentage of men with one-vessel, two-vessel, three-vessel, left main or no coronary artery disease on coronary angioraphy. Bottom: Percentage of women with one-vessel, two-vessel, three-vessel, left main, or no coronary artery disease on coronary angiography. N indicates normal or <50% stenosis; 1, one-vessel disease; 2, two-vessel disease; 3, three-vessel disease; LM, left main disease. Data from Douglas and Hurst.

Table 1.11 Properties of beta-blockers in clinical use

Drugs	Selectivity	Partial agonist activity	Usual dose for angina
Propranolol	None	No	20–80 mg twice daily
Metoprolol	β_1	No	50–200 mg twice daily
Atenolol	β_1	No	50–200 mg/day
Nadolol	None	No	40–80 mg/day
Timolol	None	No	10 mg twice daily
Acebutolol	β_1	Yes	200–600 mg twice daily
Betaxolol	β_1	No	10–20 mg/day
Bisoprolol	β_1	No	10 mg/day
Esmolol (intravenous)	β_1	No	50–300 mcg/kg/min
Labetalol*	None	Yes	200–600 mg twice daily
Pindolol	None	Yes	2.5–7.5 mg 3 times daily

* Labetalol is a combined alpha- and β-blocker.

3 Coronary angiography is recommended in patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia. *(Level of Evidence: B)*

4 Coronary angiography is recommended in patients with angina and symptoms and signs of CHF. *(Level of Evidence: C)*

5 Coronary angiography is recommended in patients with clinical characteristics that indicate a high likelihood of severe CAD. *(Level of Evidence: C)*

6 Coronary angiography is recommended in patients with stable angina in patients who are being considered for major noncardiac surgery, especially vascular surgery (repair of aortic aneurysm, femoral bypass, carotid endarterectomy) with intermediate or high risk features on noninvasive testing. *(Level of Evidence: B)*

Class IIa

1 Coronary angiography is reasonable in patients with significant LV dysfunction (ejection fraction less than 45%), CCS class I or II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing. *(Level of Evidence: C)*

2 Coronary angiography is reasonable in patients with inadequate prognostic information after noninvasive testing. *(Level of Evidence: C)*

3 Coronary angiography is reasonable in patients with a high risk of restenosis after PCI, if PCI has been performed in a prognostically important site. *(Level of Evidence: C)*

Class IIb

1 Coronary angiography may be considered in patients with CCS class I or II angina, preserved LV function (ejection fraction greater than 45%), and less than high-risk criteria on noninvasive testing. *(Level of Evidence: C)*

2 Coronary angiography may be considered in patients with CCS class III or IV angina, which with medical therapy improves to class I or II. *(Level of Evidence: C)*

3 Coronary angiography may be considered in patients with CCS class I or II angina but intolerance (unacceptable side effects) to adequate medical therapy. *(Level of Evidence: C)*

Class III

1 Coronary angiography is not recommended in patients with CCS class I or II angina who respond to medical therapy and who have no evidence of ischemia on noninvasive testing. *(Level of Evidence: C)*

2 Coronary angiography is not recommended in patients who prefer to avoid revascularization. *(Level of Evidence: C)*

Recommendations for investigation in patients with the classical triad of Syndrome X

Class I

A resting echocardiogram is recommended in patients with angina and normal or non-obstructed

coronary arteries to assess for presence of ventricular hypertrophy and/or diastolic dysfunction. *(Level of Evidence: C)*

Class IIb

1 Intracoronary acetylcholine is reasonable during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent coronary flow reserve, and exclude vasospasm. *(Level of Evidence: C)*

2 Intracoronary ultrasound, coronary flow reserve, or fractional flow reserve are reasonable measurements to exclude missed obstructive lesions, if angiographic appearances are suggestive of a non-obstructive lesion rather than completely normal, and stress imaging techniques identify an extensive area of ischaemia. *(Level of Evidence: C)*

Treatment

A. Pharmacologic therapy

Recommendations for pharmacotherapy to prevent MI and death and to reduce symptoms

Class I

1 Aspirin should be started at 75 to 162 mg per day (75 mg per day in ESC guideline) and continued indefinitely in all patients unless contraindicated. *(Level of Evidence: A)*

2 Beta-blockers as initial therapy is recommended to reduce symptoms in the absence of contraindications in patients with prior MI *(Level of Evidence: A)* or without prior MI. *(Level of Evidence: B)*

Test the effects of a beta-1 blocker, and titrate to full dose; consider the need for 24 h protection against ischemia. *(Level of Evidence: A)* (Table 1.12).

3 It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. *(Level of Evidence: A)*

4 ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction less than or equal to 40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. *(Level of Evidence: A)*

5 ACE inhibitors should be started and continued indefinitely in patients who are not lower risk (lower risk defined as those with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated. *(Level of Evidence: B)*

Table 1.12 Nitroglycerin and nitrates in angina

Compound	Route	Dose	Duration of effect
Nitroglycerin	Sublingual tablets	0.3–0.6 mg up to 1.5 mg	$1^1/_2$–7 min
	Spray	0.4 mg as needed	Similar to sublingual tablets
	Ointment	2% 6 × 6 in., 15 × 15 cm 7.5–40 mg	Effect up to 7 h
	Transdermal	0.2–0.8 mg/h every 12 h	8–12 h during intermittent therapy
	Oral sustained release	2.5–13 mg	4–8 h
	Buccal	1–3 mg 3 times daily	3–5 h
	Intravenous	5–200 mcg/min	Tolerance in 7–8 h
Isosorbide dinitrate	Sublingual	2.5–15 mg	Up to 60 min
	Oral	5–80 mg, 2–3 times daily	Up to 8 h
	Spray	1.25 mg daily	2–3 min
	Chewable	5 mg	2–$2^1/_2$ h
	Oral slow release	40 mg 1–2 daily	Up to 8 h
	Intravenous	1.25–5.0 mg/h	Tolerance in 7–8 h
	Ointment	100 mg/24 h	Not effective
Isosorbide mononitrate	Oral	20 mg twice daily 60–240 mg once daily	12–24 h
Pentaerythritol tetranitrate	Sublingual	10 mg as needed	Not known
Erythritol tetranitrate	Sublingual	5–10 mg as needed	Not known
	Oral	10–30 3 times daily	Not known

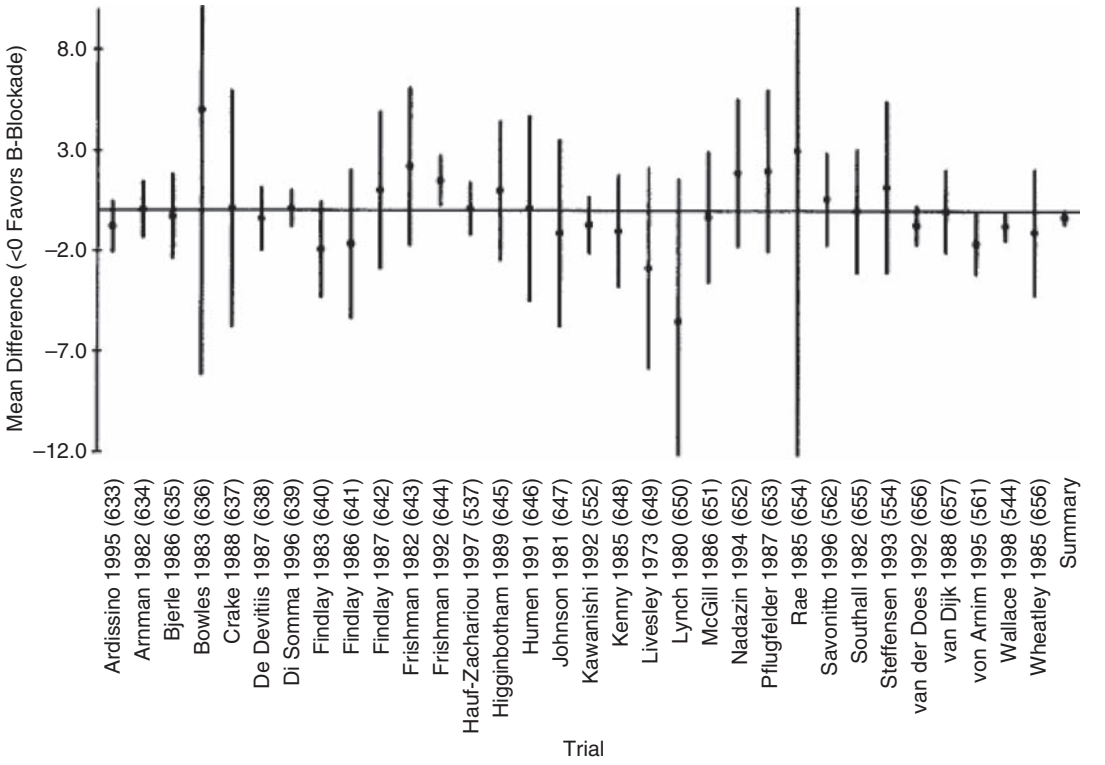

Fig. 1.3 Beta-blockers versus calcium antagonists: angina relief.
Source: Heidenreich PA, for the UCSF-Stanford Evidence-based Practice Center (AHCPR).

6 Sublingual nitroglycerin or nitroglycerin spray is recommended for the immediate relief of angina. *(Level of Evidence: B)*

7 Calcium antagonists or long-acting nitrates is recommended as initial therapy for reduction of symptoms when beta-blockers are contraindicated. *(Level of Evidence: B)* (Figure 1.3)

8 Calcium antagonists or long-acting nitrates is recommended in combination with beta-blockers when initial treatment with beta-blockers is not successful. *(Level of Evidence: B)* In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a calcium channel blocker *(Level of Evidence: A)*, long acting nitrate *(Level of Evidence: C), or* nicorandil. *(Level of Evidence: C)* (Tables 1.13 and 1.14).

9 If the effects of beta-blocker monotherapy are insufficient, add a dihydropyridine calcium channel blocker. *(Level of Evidence: B)*

10 Calcium antagonists and long-acting nitrates are recommended as a substitute for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects. *(Level of Evidence: C)*

11 Angiotensin receptor blockers are recommended for patients who have hypertension, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had a myocardial infarction with left ventricular ejection fraction less than or equal to 40%. *(Level of evidence: A)*

12 Aldosterone blockade is recommended for use in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a beta blocker, have a left ventricular ejection fraction less than or equal to 40%, and have either diabetes or heart failure. (*Level of Evidence: A)*

Table 1.13 Recommended drug therapy (calcium antagonist vs. beta-blocker) in patients with angina and associated conditions

Condition	Recommended treatment (and alternative)	Avoid
Medical conditions		
Systemic hypertension	Beta-blockers (calcium antagonists)	
Migraine or vascular headaches	Beta-blockers (verapamil or diltiazem)	
Asthma or chronic obstructive pulmonary disease with bronchospasm	Verapamil or diltiazem	Beta-blockers
Hyperthyroidism	Beta-blockers	
Raynaud's syndrome	Long-acting slow-release calcium antagonists	Beta-blockers
Insulin-dependent diabetes mellitus	Beta-blockers (particularly if prior MI) or long-acting slow-release calcium antagonists	
Non-insulin–dependent diabetes mellitus	Beta-blockers or long-acting slow-release calcium antagonists	
Depression	Long-acting slow-release calcium antagonists	Beta-blockers
Mild peripheral vascular disease	Beta-blockers or calcium antagonists	
Severe peripheral vascular disease with rest ischemia	Calcium antagonists	Beta-blockers
Cardiac arrhythmias and conduction abnormalities		
Sinus bradycardia	Long-acting slow-release calcium antagonists that do not decrease heart rate	Beta-blockers, verapamil, diltiazem
Sinus tachycardia (not due to heart failure)	Beta-blockers	
Supraventricular tachycardia	Verapamil, diltiazem, or beta-blockers	
Atrioventricular block	Long-acting slow-release calcium antagonists that do not slow A-V conduction	Beta-blockers, verapamil, diltiazem
Rapid atrial fibrillation (with digitalis)	Verapamil, diltiazem, or beta-blockers	
Ventricular arrhythmias	Beta-blockers	
Left ventricular dysfunction		
Congestive heart failure		
Mild (LVEF ≥ 40%)	Beta-blockers	
Moderate to severe (LVEF < 40%)	Amlodipine or felodipine (nitrates)	Verapamil, diltiazem
Left-sided valvular heart disease		
Mild aortic stenosis	Beta-blockers	
Aortic insufficiency	Long-acting slow-release dihydropyridines	
Mitral regurgitation	Long-acting slow-release dihydropyridines	
Mitral stenosis	Beta-blockers	
Hypertrophic cardiomyopathy	Beta-blockers, non-dihydropyridine calcium antagonist	Nitrates, dihydropyridine calcium antagonists

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction.

Table 1.14 Randomized controlled trials examining the effects of exercise training on exercise capacity in patients with stable angina

First author	N	Men (%)	Setting	Intervention	F/C	Outcome
Ornish	46	N/A	Res	M	24 d	↑ ex. tolerance
Froelicher	146	100	OR	E	1 y	↑ ex. tolerance ↑ O_2 consumption
May	121	N/A	OR	E	10–12 mo	↑ O_2 consumption ↑ max HR-BP
Sebrechts	56	100	OR	E	1 y	↑ ex. duration
Oldridge	22	100	OR/H	E	3 mo	↑ O_2 consumption
Schuler	113	100	OR	M	1 y	↑ work capacity ↑ max HR-BP
Hambrecht	88	100	Hosp/H	M	1 y	↑ O_2 consumption ↑ ex. duration
Fletcher	88 Disabled	100	H	E	6 mo	NS (ex. duration or O_2 consumption)
Haskell	300	86	H	M	4 y	↑ ex. tolerance

Res indicates Residential facility. OR, Outpatient rehab; H, home; Hosp, Hospital; M, Multifactorial; E, Exercise training only; ↑, Statistically significant increase favoring intervention; NS, No significant difference between groups; N/A, Not available.

13 An annual influenza vaccination is recommended for patient with cardiovascular disease. (*Level of Evidence: B*)
14 Lipid management – see subsequent recommendations for treatment of risk factors.

Class IIa

1 Clopidogrel is reasonable when aspirin is absolutely contraindicated. *(Level of Evidence: B)*
2 Long-acting nondihydropyridine calcium antagonists are reasonable instead of beta-blockers as initial therapy. *(Level of Evidence: B)*
3 It is reasonable to use ACE inhibitors among lower-risk patients with mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed. *(Level of Evidence: B)*
4 High-dose statin therapy is reasonable in high risk (>2% annual CV mortality) patients with proven coronary disease. *(Level of Evidence: B)*
5 In cases of beta-blocker intolerance try sinus node inhibitor *(Level of Evidence: B)*
6 If calcium channel blocker (CCB) monotherapy or combination therapy (CCB with beta-blocker) is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil. Be careful to avoid nitrate tolerance. *(Level of Evidence C)*

Class IIb

1 Low-intensity anticoagulation with warfarin may be considered in addition to aspirin. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. *(Level of Evidence: B)*
2 Angiotensin receptor blockers may be considered in combination with ACE inhibitors for heart failure due to left ventricular systolic dysfunction. *(Level of Evidence: B)*
3 Fibrate therapy may be considered in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome. *(Level of Evidence: B)*
4 Fibrate or nicotinic acid as adjunctive therapy to statin may be considered in patients with low HDL and high triglycerides at high risk (>2% annual CV mortality). *(Level of Evidence: C)*
5 Metabolic agents may be used where available as add on therapy, or as substitution therapy when conventional drugs are not tolerated. *(Level of Evidence: B)*

Class III

1 Dipyridamole is not recommended. *(Level of Evidence: B)*

2 Chelation therapy (intravenous infusions of ethylenediamine tetraacetic acid of EDTA) is not recommended for the treatment of chronic angina or arteriosclerotic cardiovascular disease and may be harmful because of its potential to cause hypocalcemia. *(Level of Evidence: C)*

Recommendations for pharmacological therapy to improve symptoms in patients with Syndrome X

Class I

1 Therapy with nitrates, beta-blockers, and calcium antagonists alone or in combination are recommended. *(Level of Evidence: B)*

2 Statin therapy in patients with hyperlipidemia is recommended. *(Level of Evidence: B)*

3 ACE-inhibition in patients with hypertension is recommended. *(Level of Evidence: C)*

Class IIa

Trial of therapy with other anti-anginals including nicorandil and metabolic agents is reasonable. *(Level of Evidence: C)*

Class IIb

1 Aminophylline for continued pain despite Class I measures may be considered. *(Level of Evidence: C)*

2 Imipramine for continued pain despite Class I measures may be considered. *(Level of Evidence: C)*

Recommendations for pharmacological therapy of vasospastic angina

Class I

Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions is recommended. *(Level of Evidence: B)*

Coronary disease risk factors and evidence that treatment can reduce the risk for coronary disease events

Recommendations for treatment of risk factors

Class I

1 Patients should initiate and/or maintain lifestyle modification-weight control; increased physical activity; moderation of alcohol consumption; limited sodium intake; and maintenance of a diet high in fresh fruits, vegetables, and low-fat dairy products. *(Level of Evidence: B)*

2 Blood pressure control according to Joint Nation Conference VII guidelines is recommended (i.e., blood pressure less than 140/90 mm Hg or less than 130/80 mm Hg for patients with diabetes or chronic kidney disease). *(Level of Evidence: A)*

3 For hypertensive patients with well established coronary artery disease, it is useful to add blood pressure medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve target blood pressure. *(Level of Evidence: C)*

4 Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home is recommended. Follow-up, referral to special programs, and/or pharmacotherapy (including nicotine replacement) is recommended, as is a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange). *(Level of Evidence: B)*

5 Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal HbA_{1c}. (*Level of Evidence: B)*

6 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. *(Level of Evidence: B)*

7 Physical activity of 30 to 60 minutes, 7 days per week (minimum 5 days per week) is recommended. All patients should be encouraged to obtain 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by an increase in daily activities (such as walking breaks at work, gardening, or household work). *(Level of Evidence: B)*.

8 The patient's risk should be assessed with a physical activity history. Where appropriate, an exercise test is useful to guide the exercise prescription. *(Level of Evidence: B)*

9 Medically supervised programs (cardiac rehabilitation) are recommended for at-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure). *(Level of Evidence: B)*

10 Dietary therapy for all patients should include reduced intake of saturated fats (to less than 7% of

total calories), trans-fatty acids, and cholesterol (to less than 200 mg per day). *(Level of Evidence: B)*

11 Daily physical activity and weight management are recommended for all patients. *(Level of Evidence: B)*

12 Recommended lipid management includes assessment of a fasting lipid profile. *(Level of Evidence: A)*

13 LDL-C should be less than 100 mg per dL. *(Level of Evidence: A)*

14 If baseline LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy should be initiated in addition to therapeutic lifestyle changes. When LDL-lowering medications are used in high-risk or moderately high-risk persons, it is recommended that intensity of therapy be sufficient to achieve a 30% to 40% reduction in LDL-C levels. *(Level of Evidence: A)*

15 If on treatment LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy should be intensified. (*Level of Evidence: A)*

16 If TG are 200 to 499 mg per dL, non-HDL-C should be less than 130 mg per dL. *(Level of Evidence: A)*

17 BMI and waist circumference should be assessed regularly. On each patient visit, it is useful to consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to achieve and maintain a BMI between 18.5 and 24.9 kg/m^2. *(Level of Evidence: B)*

18 If waist circumference is greater than or equal to 35 inches (89 cm) in women or greater than or equal to 40 inches (102 cm) in men it is beneficial to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 37 to 40 inches (94 to 102 cm). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference. *(Level of Evidence: B)*

19 The initial goal of weight loss therapy should be to gradually reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. *(Level of Evidence: B)*

Class IIa

1 Adding plant stanol/sterols (2 g per day) and/or viscous fiber (greater than 10 g per day) is reasonable to further lower LDL-C. *(Level of Evidence: A)*

2 Reduction of LDL-C to less than 70 mg per dL or high-dose statin therapy is reasonable. *(Level of Evidence: A)*

3 If baseline LDL-C is 70 to 100 mg per dL, it is reasonable to treat LDL-C to less than 70 mg per dL. *(Level of Evidence: B)*

4 Further reduction of non-HDL-C to less than 100 mg per dL is reasonable.

5 If TG are greater than or equal to 200 to 499 mg per dL therapeutic options to reduce non-HDL-C are:

a. niacin can be useful as a therapeutic option to reduce non-HDL-C (after LDL-C-lowering therapy) or

b. fibrate therapy as a therapeutic option can be useful to reduce non-HDL-C (after LDL-C lowering therapy. *(Level of Evidence: B)*

6 The following lipid management strategies can be beneficial: If LDL-C less than 70 mg per dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C less than 70 mg per dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of greater than 50% in LDL-C levels by either statins or LDL-C-lowering drug combinations.*(Level of Evidence: C)*

Class IIb

1 Folate therapy may be considered in patients with elevated homocysteine levels. *(Level of Evidence: C)*

2 Identification and appropriate treatment of clinical depression may be considered to improve CAD outcomes. *(Level of Evidence: C)*

3 Intervention directed at psychosocial stress reduction may be considered. *(Level of Evidence: C)*

4 Expanding physical activity to include resistance training on 2 days per week may be reasonable. *(Level of Evidence: C)*

5 For all patients, encouraging consumption of omega-T 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 TG, higher doses are usually necessary for risk reduction. *(Level of Evidence: B)*

Class III

1 Initiation of hormone replacement therapy in postmenopausal women is not recommended for the purpose of reducing cardiovascular risk. *(Level of Evidence: A)*

2 Vitamin C and E supplementation is not recommended. *(Level of Evidence: A)*

3 Chelation therapy (intravenous infusions of ethylenediamine tetraacetic acid of EDTA) is not recommended for the treatment of chronic angina or arteriosclerotic cardiovascular disease and may be harmful because of its potential to cause hypocalcemia. *(Level of Evidence: C)*

4 Garlic is not recommended. *(Level of Evidence: C)*

5 Acupuncture is not recommended. *(Level of Evidence: C)*

6 Coenzyme Q is not recommended. *(Level of Evidence: C)*

Recommendations for revascularization with PCI (or other catheter-based techniques) and CABG in patients with stable angina

Class I

1 Coronary artery bypass grafting is recommended for patients with significant left main coronary disease. *(Level of Evidence: A)*

2 Coronary artery bypass grafting is recommended for patients with three-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction less than 50%). *(Level of Evidence: A)*

3 Coronary artery bypass grafting is recommended for patients with two-vessel disease with significant proximal LAD CAD and either abnormal LV function (ejection fraction less than 50%) or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)*

4 CABG is recommended for significant disease with impaired LV function and viability demonstrated by noninvasive testing. *(Level of Evidence: B)*

5 Percutaneous coronary intervention is recommended for patients with two- or three-vessel disease with significant proximal LAD CAD, who have anatomy suitable for catheter-based therapy and normal LV function and who do not have treated diabetes. *(Level of Evidence: B)*

6 Percutaneous coronary intervention or CABG is recommended for patients with one- or two-vessel CAD without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*

7 Coronary artery bypass grafting is recommended for patients with one- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: C)*

8 In patients with prior PCI, CABG or PCI is recommended for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing. *(Level of Evidence: C)*

9 Percutaneous coronary intervention or CABG is recommended for patients who have not been successfully treated by medical therapy (see text) and can undergo revascularization with acceptable risk. *(Level of Evidence: B)*

Class IIa

1 Repeat CABG is reasonable for patients with multiple saphenous vein graft stenoses, especially when there is significant stenosis of a graft supplying the LAD. It may be appropriate to use PCI for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery. *(Level of Evidence: C)*

2 Use of PCI or CABG is reasonable for patients with one- or two-vessel CAD without significant proximal LAD disease but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing. *(Level of Evidence: B)*

3 Use of PCI or CABG is reasonable for patients with one-vessel disease with significant proximal LAD disease. *(Level of Evidence: B)*

4 CABG is reasonable for single- or two-vessel CAD without significant proximal LAD stenosis in patients who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: B)*

5 CABG is reasonable for significant three vessel disease in diabetics with reversible ischaemia on functional testing. *(Level of Evidence: C)*

6 PCI or CABG is reasonable for patients with reversible ischaemia on functional testing and evidence of frequent episodes of ischaemia during daily activities. *(Level of Evidence: C)*

Class IIb

1 Compared with CABG, PCI may be considered for patients with two- or three-vessel disease with significant proximal LAD CAD, who have anatomy suitable for catheter-based therapy, and who have treated diabetes or abnormal LV function. *(Level of Evidence: B)*

2 Use of PCI may be considered for patients with significant left main coronary disease who are not candidates for CABG. *(Level of Evidence: C)*

3 PCI may be considered for patients with one- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: C)*

Class III

1 Use of PCI or CABG is not recommended for patients with one- or two vessel CAD without significant proximal LAD CAD, who have mild symptoms that are unlikely due to myocardial ischemia, or who have not received an adequate trial of medical therapy and

a. have only a small area of viable myocardium or

b. have no demonstrable ischemia on noninvasive testing. *(Level of Evidence: C)*

2 Use of PCI or CABG is not recommended for patients with borderline coronary stenoses (50% to 60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing. *(Level of Evidence: C)*

3 Use of PCI or CABG is not recommended for patients with insignificant coronary stenosis (less than 50% diameter). *(Level of Evidence: C)*

4 Use of PCI is not recommended in patients with significant left main coronary artery disease who are candidates for CABG. *(Level of Evidence: B)*

Recommendations for revascularization to improve symptoms in patients with stable angina

Class I

1 CABG for multi-vessel disease (MVD) technically suitable for surgical revascularization is recommended in patients with moderate to severe symptoms not controlled by medical therapy, in whom risks of surgery do not outweigh potential benefits. *(Level of Evidence: A)*

2 PCI for single vessel disease technically suitable for percutaneous revascularization is recommended in patients with moderate to severe symptoms not controlled by medical therapy, in whom procedural risks do not outweigh potential benefits. *(Level of Evidence: A)*

3 PCI for MVD without high risk coronary anatomy, technically suitable for percutaneous revascularization is recommended in patients with moderate to severe symptoms not controlled by medical therapy and in whom procedural risks do not outweigh potential benefits. *(Level of Evidence: A)*

Class IIa

1 PCI for single vessel disease technically suitable for percutaneous revascularization is reasonable in patients with mild to moderate symptoms which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits. *(Level of Evidence: A)*

2 CABG for single vessel disease technically suitable for surgical revascularization is reasonable in patients with moderate to severe symptoms not controlled by medical therapy, in whom operative risk does not outweigh potential benefit. *(Level of Evidence: A)*

3 CABG in MVD technically suitable for surgical revascularization is reasonable in patients with mild to moderate symptoms, which are nonetheless unacceptable to the patient, in whom operative risk does not outweigh potential benefit. *(Level of Evidence: A)*

4 PCI for MVD technically suitable for percutaneous revascularization is reasonable in patients with mild to moderate symptoms, which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits. *(Level of Evidence: A)*

Class IIb

CABG in single vessel disease technically suitable for surgical revascularization may be considered in patients with mild-to-moderate symptoms, which are nonetheless unacceptable to the patient, in whom operative risk is not greater than estimated annual mortality. *(Level of Evidence: B)*

Recommendations for alternative therapies for chronic stable angina in patients refractory to medical therapy who are not candidates for percutaneous intervention or surgical revascularization

Class IIa

Surgical laser transmyocardial revascularization is reasonable. *(Level of Evidence: A)*

Class IIb

1 Enhanced external counterpulsation may be considered. *(Level of Evidence: B)*

2 Spinal cord stimulation may be considered. *(Level of Evidence: B)*

Patient follow-up: monitoring of symptoms and anti-anginal therapy

Recommendations for echocardiography, treadmill exercise testing, stress radionuclide imaging, stress echocardiography studies, and coronary angiography during patient follow-up

Class I

1 A chest X-ray is recommended for patients with evidence of new or worsening CHF. *(Level of Evidence: C)*

2 Assessment of LV ejection fraction and segmental wall motion by echocardiography or radionuclide imaging is recommended in patients with new or worsening CHF or evidence of intervening MI by history or ECG. *(Level of Evidence: C)*

3 Echocardiography is recommended for evidence of new or worsening valvular heart disease. *(Level of Evidence: C)*

4 Treadmill exercise test is recommended for patients without prior revascularization who have a significant change in clinical status, are able to exercise, and do not have any of the ECG abnormalities listed below in number 5. *(Level of Evidence: C)*

5 Stress radionuclide imaging or stress echocardiography procedures are recommended for patients without prior revascularization who have a significant change in clinical status and are unable to exercise or have one of the following ECG abnormalities:

a. Pre-excitation (Wolff–Parkinson–White) syndrome. *(Level of Evidence: C)*

b. Electronically paced ventricular rhythm. *(Level of Evidence: C)*

c. More than 1 mm of rest ST depression. *(Level of Evidence: C)*

d. Complete left bundle-branch block. *(Level of Evidence: C)*

6 Stress radionuclide imaging or stress echocardiography procedures are recommended for patients who have a significant change in clinical status and required a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results. *(Level of Evidence: C)*

7 Stress radionuclide imaging or stress echocardiography procedures are recommended for patients with prior revascularization who have a significant change in clinical status. *(Level of Evidence: C)*

8 Coronary angiography is recommended in patients with marked limitation of ordinary activity (CCS class III) despite maximal medical therapy. *(Level of Evidence: C)*

Class IIb

Annual treadmill exercise testing may be considered in patients who have no change in clinical status, can exercise, have none of the ECG abnormalities listed in number 5, and have an estimated annual mortality rate greater than 1%. *(Level of Evidence: C)*

Class III

1 Echocardiography or radionuclide imaging is not recommended for assessment of LV ejection fraction and segmental wall motion in patients with a normal ECG, no history of MI, and no evidence of CHF. *(Level of Evidence: C)*

2 Repeat treadmill exercise testing is not recommended in less than three years in patients who have no change in clinical status and an estimated annual mortality rate less than 1% on their initial evaluation, as demonstrated by one of the following:

a. Low-risk Duke treadmill score (without imaging). *(Level of Evidence: C)*

b. Low-risk Duke treadmill score with negative imaging. *(Level of Evidence: C)*

c. Normal LV function and a normal coronary angiogram. *(Level of Evidence: C)*

d. Normal LV function and insignificant CAD. *(Level of Evidence: C)*

3 Stress imaging or echocardiography is not recommended for patients who have no change in clinical status and a normal rest ECG, are not taking digoxin, are able to exercise, and did not require a stress imaging or echocardiographic procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results. *(Level of Evidence: C)*
4 Repeat coronary angiography is not recommended in patients with no change in clinical status, no change on repeat exercise testing or stress imaging, and insignificant CAD on initial evaluation. *(Level of Evidence: C)*

Future issues

Since publication of these guideline recommendations in 2002, important new evidence has been published. As a result of this new evidence, the next revision of the guidelines, which is currently underway, will likely reflect changes in the following areas:

Special consideration for women

Recent evidence, particularly from the NHLBI-sponsored Women's Ischemic Syndrome Evaluation (WISE) Study [5,6], has suggested that traditional approaches significantly underestimate the presence of obstructive CAD in women, particularly younger women. Moreover, many women without obstructive disease continue to have symptoms and a poor quality of life [7,8]. Many have evidence of microvascular dysfunction [9]. There is growing interest in the development of gender-specific tools for the assessment of ischemic heart disease in women, but the evidence is not yet robust enough to support the widespread use of a new approach.

New information on percutaneous revascularization to be considered for the next chronic stable angina guideline

As listed above, the 2002 guidelines included a Class I recommendation for PCI or CABG in symptomatic or asymptomatic patients with "one- or two-vessel CAD . . . with high risk criteria on noninvasive testing." A randomized trial reported in 2007 has challenged the assumption that revascularization improves patient outcomes in many patients with multi-vessel coronary disease. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial – the largest reported randomized clinic trial on coronary artery disease to date – enrolled 2287 patients with significant coronary artery disease and inducible ischemia. In contrast to previous trials, medical therapy in the COURAGE trial focused not only on symptomatic relief, but also risk factor reduction. Medical therapy resulted in very high rates of adherence to the recommendations for blood pressure, lipid levels, exercise, diet, and smoking cessation that are detailed above. When added to such medical therapy, PCI did not provide any advantage for the primary endpoint of death or myocardial infarction. Future revisions of the stable angina clinic practice guideline will consider the results of COURAGE. Although we do not want to prejudge the careful rigorous process of guideline development, it certainly seems likely that the indications for revascularization in asymptomatic patients, and in selected symptomatic patients, are likely to be more cautious than those listed above [10–12].

New therapeutic agents to be considered for the next chronic stable angina guideline

Ranolazine is a novel therapeutic agent recently approved by the FDA for the treatment of refractory angina. It appears to reduce anginal episodes and to increase exercise tolerance without increasing cardiovascular risk despite a potential to increase the QT interval. Varenicline is a partial nicotine receptor agonist that shows great promise to help patients overcome addiction to smoking. Both of these agents will be thoroughly assessed by the next chronic stable angina writing group with a new guideline expected in late 2008 [13–18].

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 Appropriateness Criteria for Stress Echocardiography, http://circ.ahajournals.org/cgi/content/full/117/11/1478.

2 Unstable Angina/Non-ST-Elevation Myocardial Infarction

Jeffrey L. Anderson and Nanette Kass Wenger

Overview of recommendations for management of patients with UA/NSTEMI
Initial evaluation and management
a. Clinical assessment
b. Early risk stratification
c. Immediate management
Early hospital care
a. Anti-ischemic and analgesic therapy
b. Antiplatelet/anticoagulant therapy in patients for whom diagnosis of UA/NSTEMI is likely or definite
I. Antiplatelet therapy
II. Anticoagulant therapy
III. Additional management consideration
c. Initial conservative versus initial invasive strategies Risk stratification before discharge
Revascularization with PCI and CABG in patients with UA/NSTEMI
a. Percutaneous coronary intervention
b. CABG
Late hospital care, hospital discharge, and post-hospital discharge care
a. Medical regimen and use of medications
b. Long-term medical therapy and secondary prevention
I. Antiplatelet therapy
II. Beta-blockers
III. Inhibition of the renin–angiotensin–aldosterone system
IV. Nitroglycerin
V. Calcium channel blockers
VI. Lipid management
VII. Blood pressure control
VIII. Diabetes mellitus
IX. Smoking cessation
X. Weight management
XI. Physical activity
XII. Depression
b. Cardiac rehabilitation
c. Special groups: older adults
d. Special groups: chronic kidney disease
Comparison of ESC with ACC/AHA approach
Future directions

The AHA Guidelines and Scientific Statements Handbook
Edited by Valentin Fuster
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Overview of recommendations for management of patients with UA/NSTEMI

The ACC/AHA 2007 Guidelines for the Management of Patients with UA/NSTEMI place emphasis on early access to medical evaluation and initial risk assessment (see Table 2.1) [1]. New imaging modalities (coronary computed tomographic [CT] angiography and cardiac magnetic resonance imaging) are now recognized as diagnostic options in selected patients [2]. Troponins are highlighted as the dominant cardiac biomarker of necrosis (Figures 2.1, 2.2). B-type natriuretic peptides have been added to the list of biomarkers potentially useful in risk assessment [3]. Supplemental posterior ECG leads V7–V9 are noted to be a reasonable diagnostic tool to rule out MI caused by left circumflex occlusion [4].

Updated clinical trials data continue overall to support an initial invasive strategy for higher-risk and clinically unstable UA/NSTEMI patients (see Table 2.2) [5]; nevertheless, at least one trial (ICTUS) [6] suggested that an initial conservative (selective invasive) strategy may be considered in initially stabilized patients who have an elevated risk of clinical

Table 2.1 TIMI risk score for unstable angina/non-ST elevation MI

TIMI risk score	All-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 d 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 y 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 h
- Use of aspirin in prior 7 d
- Elevated serum cardiac biomarkers

*Variable remained relatively insensitive to missing information and remained a significant predictor of events.

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;284:835–42.

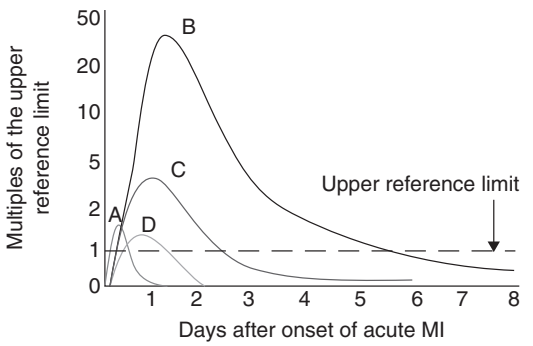


Fig. 2.1 Timing of release of biomarkers following acute myocardial infarction. Peak A, early release of myoglobin after acute MI; peak B, cardiac troponin after "classic" acute MI (frequently seen with ST-elevation MI); peak C, CK-MB after acute MI; peak D, cardiac troponin after "microinfarction" (typically seen after NSTEMI). Data are plotted on a relative scale, where 1.0 is set at the upper reference limit. AMI, acute myocardial infarction; CAD, coronary artery disease; CK, creatine kinase. Modified from WU AH, *et al.* Clin Chem. 1999;45:1104–121 and Antman EM. Decision making with cardiac troponin tests. N Engl J Med. 2002;346:2079–82.

events. An overview of emerging data suggests that an initial conservative strategy may be considered in low-risk ACS patients, and is preferred in particular in low-risk women [7–9].

The recommendation for beta-blockade in these new guidelines now is counterbalanced with a statement on the potential for harm, especially with acute IV administration in those at risk of heart failure or cardiogenic shock (COMMIT Study) [10]. Nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin should be avoided in UA/NSTEMI patients because of the recent recognition of potential harm [11,12]. Contemporary thienopyridine use (primarily with clopidogrel) is emphasized, including higher loading-dose options [13], earlier (upstream) administration, and longer duration administration (especially after drug-eluting stent placement) (see Figure 2.3) [14].

Two new anticoagulants, fondaparinux [15] and bivalirudin [16], are recommended as alternatives to unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) for specific applications (see Figures 2.4–2.7). 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 patients with baseline renal insufficiency, to prevent dosing errors leading to increased bleeding risk [17]. The guidelines also incorporate recent updates for secondary and primary prevention (Table 2.3) [18]. An

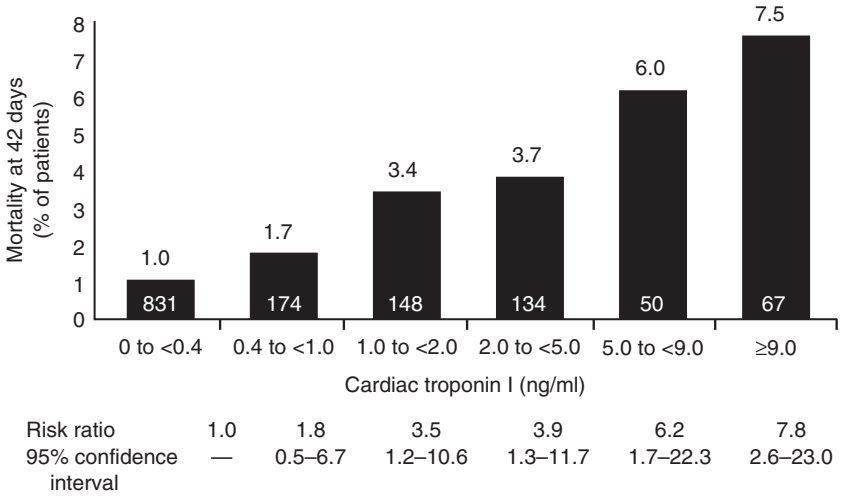


Fig. 2.2 Relationship between cardiac troponin I levels and mortality rates at 42 days (without adjustment for baseline characteristics) in patients with ACS. The numbers at the bottom of each bar are the numbers of patients with cardiac troponin I levels in each range, and the numbers above the bars are percentages. *P* less than 0.001 for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment. Used with permission 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;335:1342–9.

Table 2.2 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

expanded section recognizes special diagnostic and therapeutic considerations in special patient groups, and care processes are highlighted as important in short- and long-term patient outcomes.

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format. Selected recommendations are presented below. The reader is referred to the full-text guidelines for a complete list of the guideline recommendations as well as a presentation of the rationale and evidence supporting these recommendations with literature citations [1].

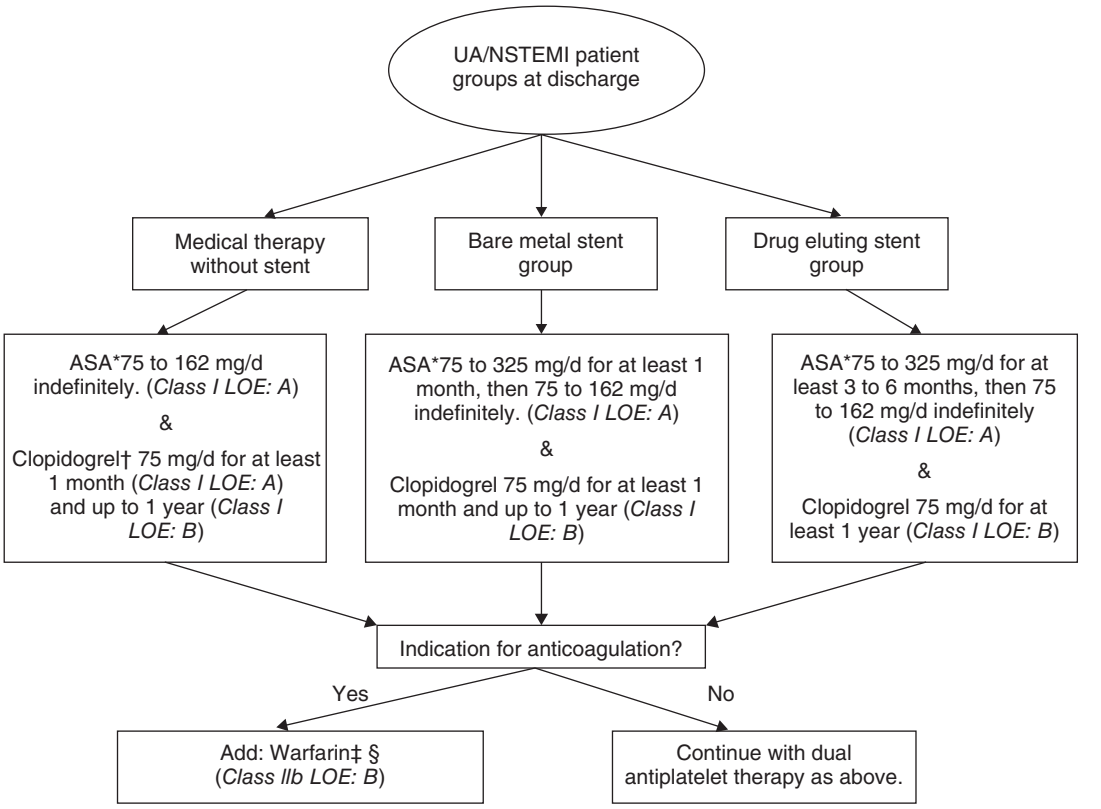


Fig. 2.3 Long-Term Antithrombotic Therapy at Hospital Discharge after UA/NSTEMI

*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 2 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.

§When warfarin is added to aspirin plus clopidogrel, an INR of 2.0 to 2.5 is recommended.

d indicates day; INR, international normalized ratio; LOE, Level of Evidence; LV, left ventricular.

Selected key ACC/AHA guidelines for management of patients with unstable angina/non-ST-elevation myocardial infarction follow.

Initial evaluation and management

a. Clinical assessment

Class I

1 Patients with 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 9-1-1 and should be transported to the hospital by ambulance rather than by friends or relatives. *(Level of Evidence: B)*

2 Prehospital EMS providers should administer 162 to 325 mg of aspirin (ASA; chewed) to chest pain patients suspected of having ACS unless contraindicated or already taken by the patient. Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. *(Level of Evidence: C)*

3 Healthcare providers should instruct patients with suspected ACS for whom nitroglycerin (NTG) has been prescribed previously to take not more than one dose of NTG sublingually in response to

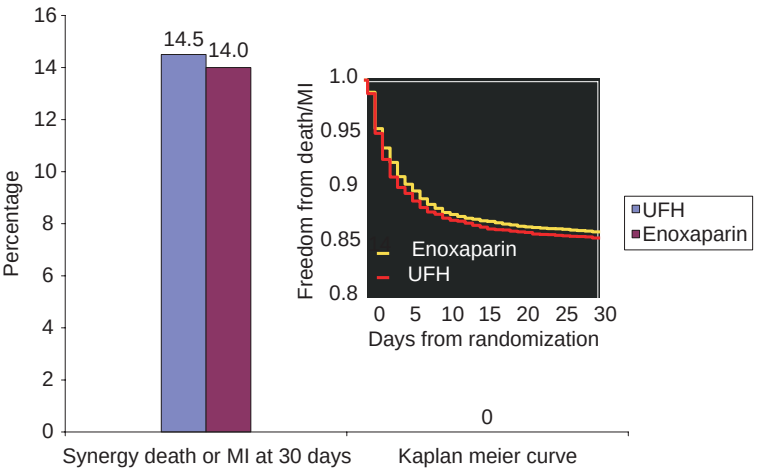
Table 2.3 Medications Used for Stabilized UA/NSTEMI Patients

Anti-ischemic and antithrombotic/antiplatelet agents	**Drug action**	**Class/level of evidence**
Aspirin	Antiplatelet	I/A
Clopidogrel* or ticlopidine	Antiplatelet when ASA contraindicated	I/A
Beta blockers	Anti-ischemic	I/B
ACEI	EF < 0.40 or HF EF > 0.40	I/A IIa/A
Nitrates	Antianginal	I/C (for ischemia)
Calcium antagonists (short-acting dihydropyridine antagonists should be avoided)	Antianginal	I for ischemic symptoms; 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 Factor	Class/Level of Evidence
HMG-CoA reductase inhibitors	LDL cholesterol > 100 mg/dL	IA
	LDL cholesterol > 70 mg/dL	IIa/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	IIa/B
Treatment of hypertension	Blood pressure > 140/90 mm Hg or > 130/80 if kidney disease or diabetes present	I/A
Treatment of diabetes	HbA1C > 7%	I/B
Hormone therapy (initiation)†	Postmenopausal state	III/A
Hormone therapy (continuation)†	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, B6, B12	Antioxidant effect; homocysteine lowering	III/A

*Preferred to ticlopidine.

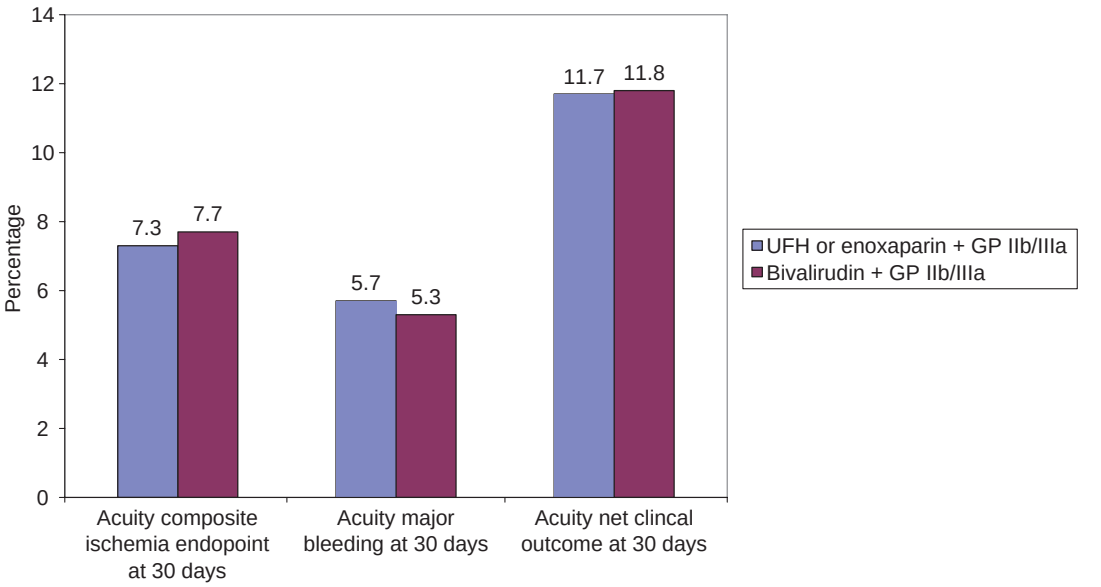
†For risk reduction of coronary artery disease.

ACEI, angiotensin-converting enzyme inhibitor (Angiotensin receptor blockers are alternatives if ACEI are not tolerated); HF, heart failure; COX-2, cyclooxygenase 2; EF, ejection fraction; HDL, high-density lipoprotein; HMG-CoA, hydroxymethyl glutaryl coenzyme A; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.



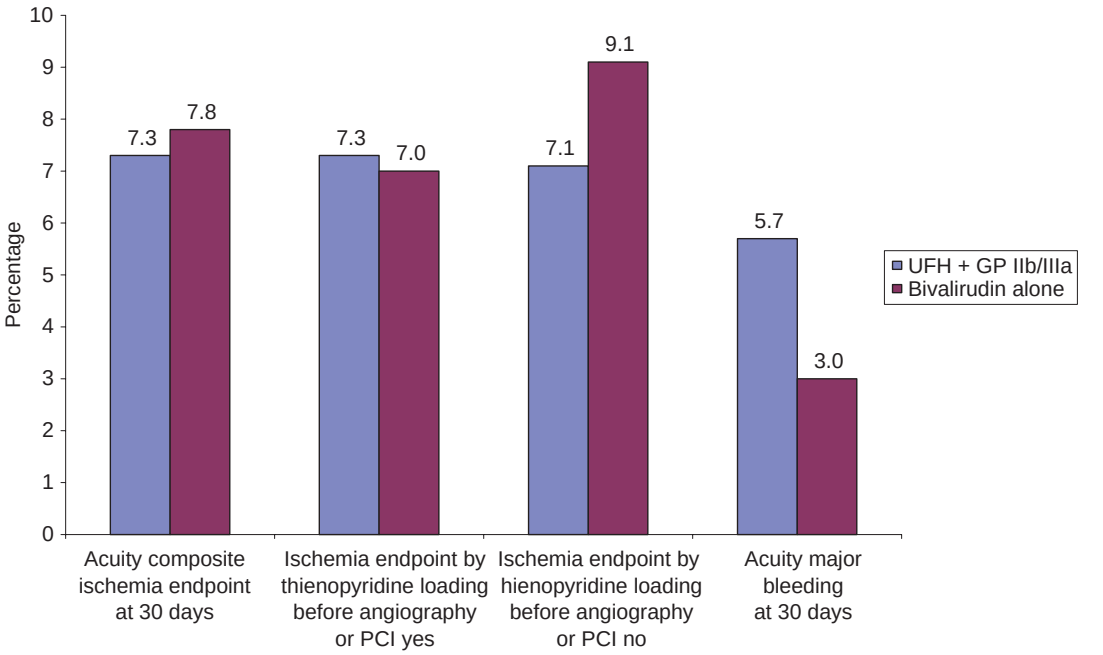
Absolute risk reduction	0.5
Hazard ratio	0.96
95% CI	0.86 to 1.06
P Value	0.40

Fig. 2.4 SYNERGY primary outcomes at 30 days.



ARR	–0.4	0.4	–0.1
Risk ratio	1.07	0.93	1.01
95% CI	0.92–1.23	0.78–1.10	0.90–1.12
P	0.007*	Less than 0.001*	Less than 0.001*

Fig. 2.5 ACUITY clinical outcomes at 30 days. *For noninferiority. ACUITY, Acute Catheterization and Urgent Intervention Triage strategy; ARR, absolute risk reduction; CI, confidence interval; GP, glycoprotein; UFH, unfractionated heparin [16].



ARR	–0.5	0.3	–2.0	2.7
RR	1.08	0.97	1.29	0.53
95% CI	0.93–1.24	0.80–1.17	1.03–1.63	0.43–0.65
P	0.32		0.054 (interaction)	Less than 0.001

Fig. 2.6 ACUITY Composite ischemia and bleeding outcomes. ACUITY, Acute Catheterization and Urgent Intervention Triage strategy; ARR, absolute risk reduction; CI, confidence interval; GP, glycoprotein; PCI, percutaneous coronary intervention; RR, relative risk [16].

chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after one NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 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/caregiver to repeat NTG every 5 min for a maximum of three doses and call 9-1-1 if symptoms have not resolved completely. *(Level of Evidence: C)*

4 Patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for greater than 20 min, 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. *(Level of Evidence: C)*

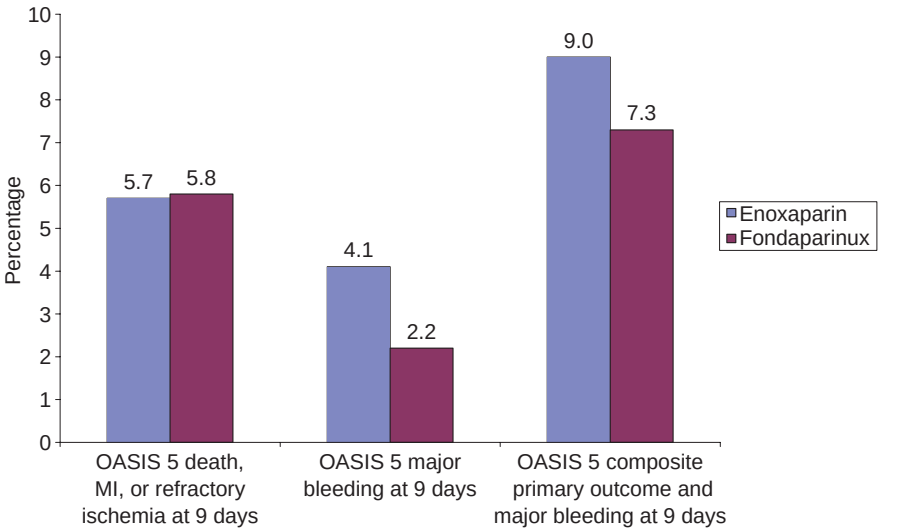
b. Early risk stratification

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. *(Level of Evidence: 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. *(Level of Evidence: B)*

3 A cardiac-specific troponin is the preferred biomarker, and if available, it should be measured in



Absolute risk reduction	–0.1	1.9	1.7
Hazard ratio	1.01	0.52	0.81
95% CI	0.90 to 1.13	0.44 to 0.61	0.73 to 0.89
P value	0.007*	less than 0.001†	less than 0.001†

**P* for noninferiority. †p for superiority. CI, confidence interval. MI, myocardial infarction. OASIS 5, Fifth Organization to Assess Strategies for Ischemic Syndromes.

Fig. 2.7 OASIS 5 Cumulative risks of death, MI or refractory ischemia [15].

all patients who present with chest discomfort consistent with ACS (see Figures 2.1, 2.2).

4 Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. *(Level of Evidence: B)* (see Figure 2.1).

Class IIa

1 Use of risk-stratification models, such as the Thrombolysis In Myocardial Infarction (TIMI) (see Table 2.1) 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. *(Level of Evidence: 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. *(Level of Evidence: B)*

Class IIb

1 For patients who present within 6 h of symptoms suggestive of ACS, a 2-h delta CK-MB mass in conjunction with 2-h delta troponin may be considered. *(Level of Evidence: B)*

2 Measurement of BNP or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. *(Level of Evidence: 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. *(Level of Evidence: 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 pharmacological) 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. *(Level of Evidence: 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/injury and hemodynamic or electrical instability. Otherwise, a telemetry step-down unit is reasonable. *(Level of Evidence: C)*

Class IIa

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. (*Level of Evidence: B*)

Early hospital care

a. Anti-ischemic and analgesic therapy

Class I

1 Bed/chair rest with continuous ECG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase. *(Level of Evidence: 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) *(Level of Evidence: B)*

3 Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of three doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. *(Level of Evidence: 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. *(Level of Evidence: B)*

5 Oral beta-blocker therapy should be initiated within the first 24 hours for patients without contraindications who do not have 1 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 s, second or third degree heart block, active asthma, or reactive airway disease). *(Level of Evidence: 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. *(Level of Evidence: B)*

7 An ACE inhibitor should be administered orally within the first 24 h 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. *(Level of Evidence: A)*

8 An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF less than or equal to 0.40. *(Level of Evidence: A)*

9 Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, nonsteroidal anti-inflammatory drugs (NSAIDs), except for ASA, whether nonselective or cyclooxygenase (COX)-2-selective agents, should be discontinued at the time a patient presents with UA/NSTEMI. *(Level of Evidence: C)*

Class IIa

1 It is reasonable to administer supplemental oxygen to all patients with UA/NSTEMI during the first 6 h after presentation. *(Level of Evidence: C)*

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* Risk factors for cardiogenic shock (the greater the number of risk factors, the higher the risk of developing cardiogenic shock): Age >70 years, SBP <120 mm Hg, ST >110 or HR <60, ↑ time since onset of symptoms of UA/NSTEMI.

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. *(Level of Evidence: 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 s, second or third degree heart block, active asthma, or reactive airway disease). *(Level of Evidence: 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. *(Level of Evidence: C)*

5 An ACE inhibitor administered orally within the first 24 h 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. *(Level of Evidence: 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. *(Level of Evidence: 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 per min), tachycardia (more than 100 beats per min) in the absence of symptomatic HF, or right ventricular infarction *(Level of Evidence: C)*

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 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. *(Level of Evidence: C)*

3 Immediate-release dihydropyridine calcium channel blockers should not be administered to patients with UA/NSTEMI in the absence of a beta-blocker. *(Level of Evidence: 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 *(Level of Evidence: A)*

5 Nonsteroidal anti-inflammatory drugs (except for ASA), 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. *(Level of Evidence: C)*

b. Antiplatelet/anticoagulant therapy in patients for whom diagnosis of UA/NSTEMI is likely or definite

Recommendations are written as the reader follows through the algorithm for Antiplatelet/Anticoagulant Therapy and Triage for Angiography (Figures 2.8, 2.9 and 2.10). Letters after recommendations refer to the specific box in the algorithm.

I. 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 of that medication. *(Level of Evidence: A)* (Figures 2.8 and 2.9; Box A).

2 Clopidogrel (loading dose followed by daily maintenance dose)† should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. *(Level of Evidence: A)* (Figures 2.8 and 2.9; Box A).

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* Risk factors for cardiogenic shock (the greater the number of risk factors, the higher the risk of developing cardiogenic shock): Age >70 years, SBP <120 mm Hg, ST >110 or HR <60, ↑ time since onset of symptoms of UA/NSTEMI.

† Some uncertainty exists about the optimal loading dose. 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 as well as safety of higher oral loading doses have not been rigorously established.

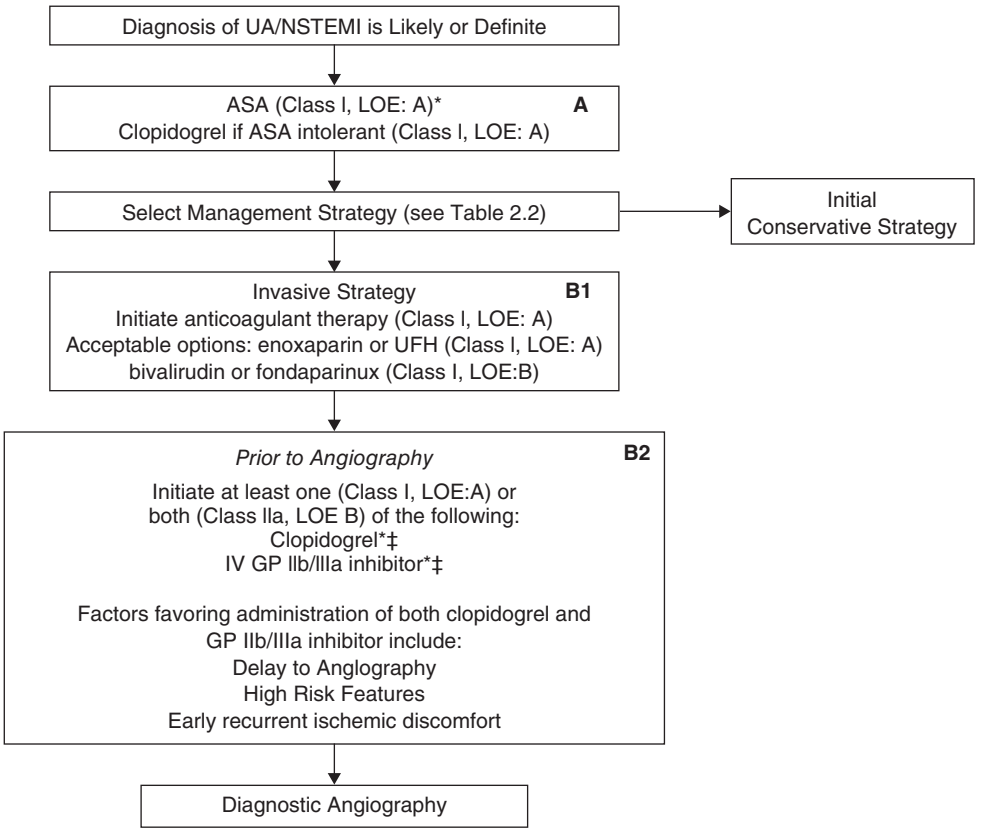

Fig. 2.8 Algorithm for patients with UA/NSTEMI managed by an initial invasive strategy.
*For dosing, see Figure 2.3 and full-text guidelines.
‡GP IIb/IIIa inhibitors may not be necessary if patient received a preloading dose of at least 300 mg clopidogrel at least 6 h earlier (Class I, LOE: B for clopidogrel administration) and bivalirudin was selected as the anticoagulant (Class IIa, LOE: B).

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. *(Level of Evidence: 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 *(Level of Evidence: A)* 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. *(Level of Evidence: 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 ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (*Level of Evidence: A*) and ideally up to 1 year *(Level of Evidence: B)* (Figure 2.9; 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 *(Level of Evidence: A)* (Figure 2.9; Box D). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; *Level of Evidence: A*) or clopidogrel (loading dose followed by daily maintenance dose; *Level of Evidence: A*) should be added to ASA and antico-agulant therapy before diagnostic angiography (upstream). *(Level of Evidence: C)*

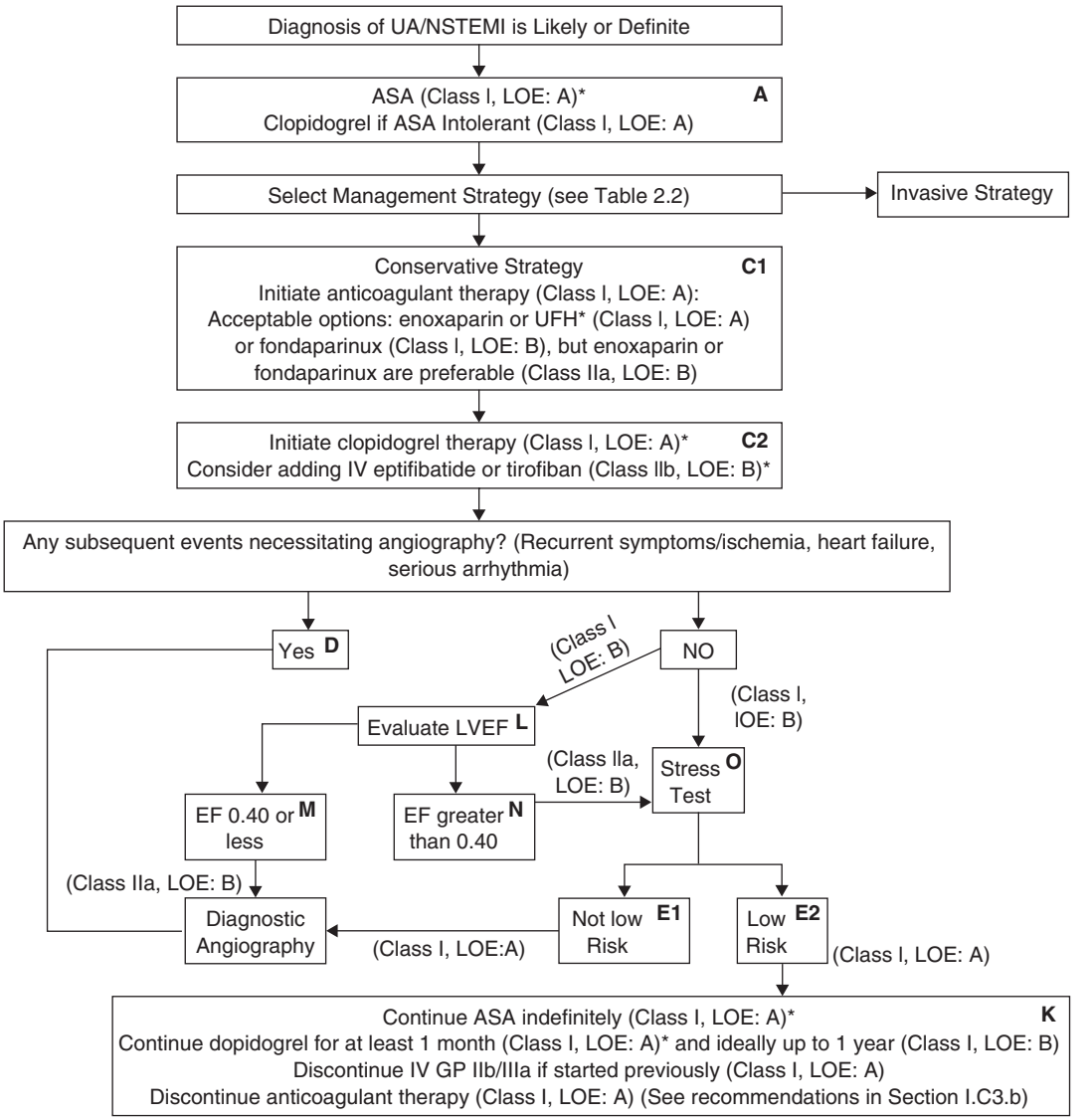

Fig. 2.9 Algorithm for patients with UA/NSTEMI managed by an initial conservative strategy.
* For dosing, see Figure 2.3 and full-text guidelines.

Class IIa

1 For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography. (*Level of Evidence: C*)

2 For UA/NSTEMI patents in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel (loading dose plus maintenance dose) and an IV GP IIb/IIIa inhibitor (*Level of Evidence: B*). Abceximab 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 (*Level of Evidence: 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 antag-

onist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier. *(Level of Evidence: B)* (see Figure 2.6).

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. *(Level of Evidence: B)*. (Figure 2.9; Box C2)

Class III

Abciximab should not be administered to patients in whom PCI is not planned. *(Level of Evidence: A)*

II. Anticoagulant therapy

Recommendations are written as the reader follows the algorithm for Antiplatelet/Anticoagulant Therapy and Triage for Angiography (Figures 2.8, 2.9 and 2.10). Letters after recommendations refer to the specific box in the algorithm.

Class I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

a. For patients in whom an invasive strategy is selected, regimens with established efficacy at a *Level of Evidence: A* include enoxaparin and UFH (Figure 2.8; Box B1; also, Figure 2.4), and those with established efficacy at a *Level of Evidence: B* include bivalirudin (Figures 2.5, 2.6) and fondaparinux (Figure 2.9; Box B1; also Figure 2.7).

b. For patients in whom an initial conservative strategy is selected, regimens using either enoxaparin* or UFH (*Level of Evidence: A)* (Figure 2.4) or fondaparinux (*Level of Evidence: B)* (Figure 2.7) have established efficacy. (Figure 2.9; Box C1)* See also class IIa recommendation below.

c. In patients in whom an initial conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable (*Level of Evidence: B*) (Figure 2.9; Box C1) (Figure 2.7).

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 coronary artery bypass graft surgery (CABG) is planned within 24 h. (*Level of Evidence: B*)

III. Additional management consideration

Class III

Intravenous fibrinolytic therapy is not indicated in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block. *(Level of Evidence: A)*

c. 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). *(Level of Evidence: 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. *(Level of Evidence: A)* (see Table 2.3, Figure 2.11).

3 In women with low-risk features, a conservative strategy is recommended. *(Level of Evidence: B)*

4 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. *(Level of Evidence: C)*

Class IIb

1 In initially stabilized patients, an initially 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. (*Level of Evidence: B)* The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made considering physician and patient preference. (*Level of Evidence: C)*

2 An invasive strategy may be reasonable in patients with chronic renal insufficiency. (*Level of Evidence: C)*

Class III

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. *(Level of Evidence: C)*

* Limited data are available for the use of other LMWHs (e.g., dalteparin) in UA/NSTEMI.

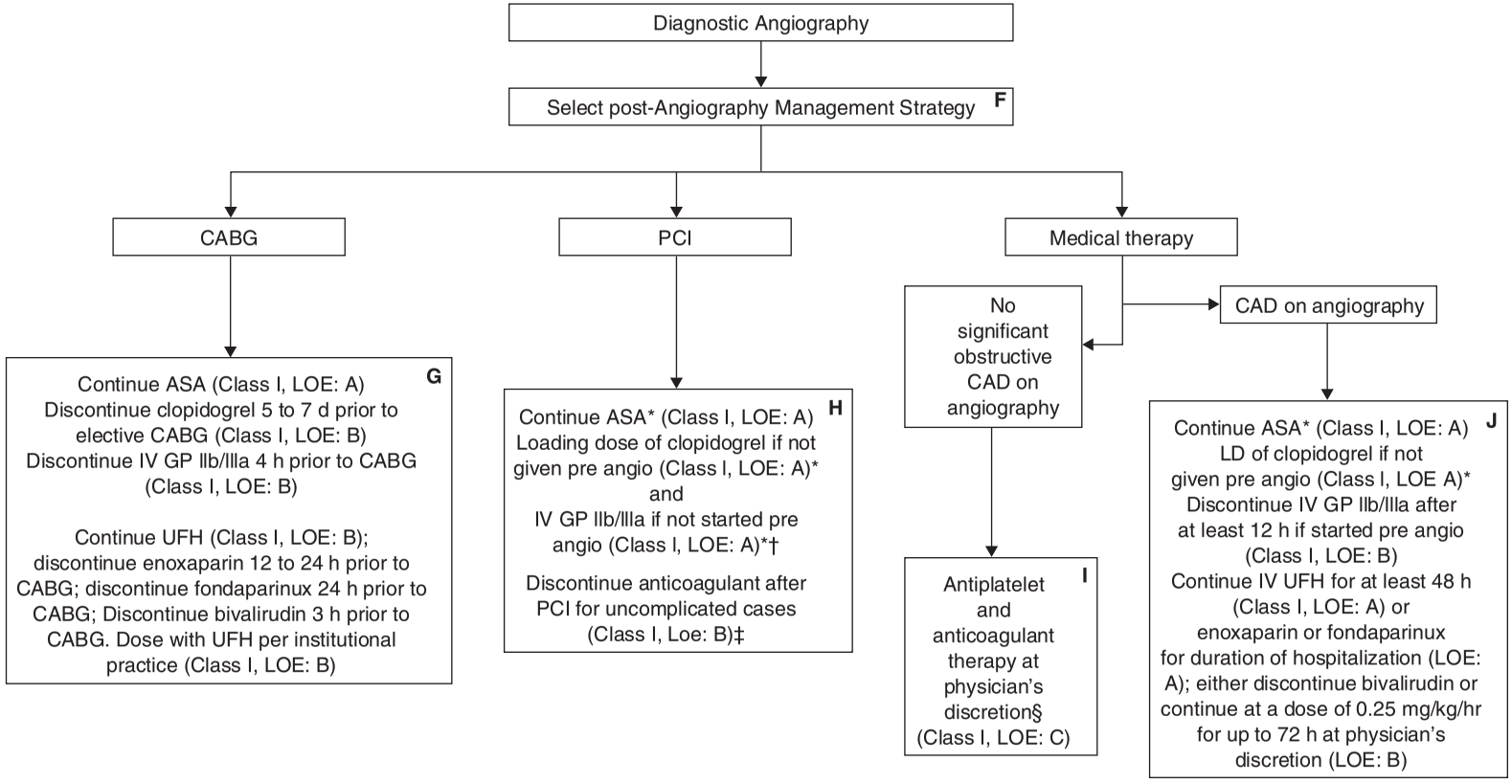

Fig. 2.10 Management after diagnostic angiography in patients with UA/NSTEMI.

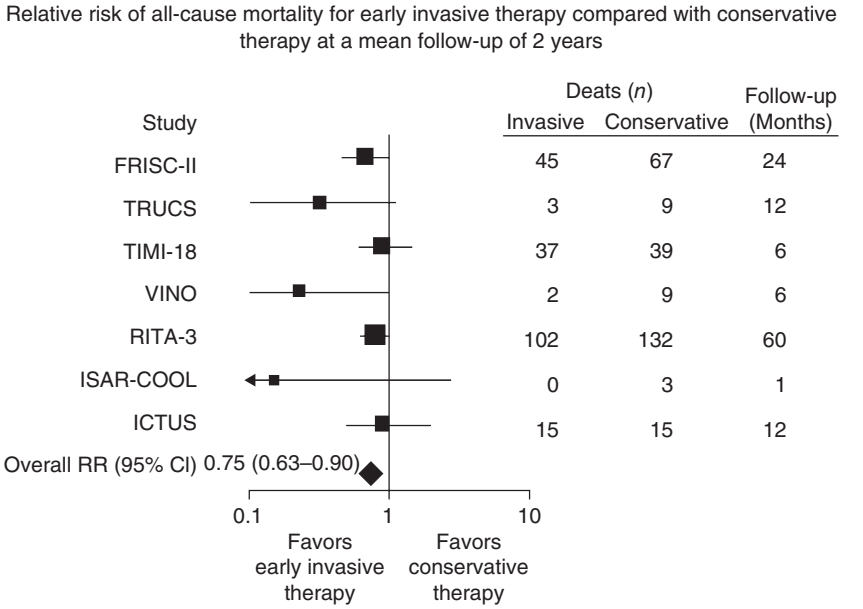

Fig. 2.11 Relative risk outcomes with early invasive vs. conservative therapy in UA/NSTEMI. From Bavry *et al.* J Am Coll Cardiol. 2006;48:1319–25.

Risk stratification before discharge

Class I

1 Noninvasive stress testing is recommended in low-risk patients who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h. *(Level of Evidence: C)*

2 Noninvasive stress testing is recommended in patients at intermediate risk who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h. *(Level of Evidence: C)*

3 An imaging modality should be added in patients with resting ST-segment depression (greater than or equal to 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 Pharmacological stress testing with imaging is recommended when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or general debility) preclude adequate exercise stress. *(Level of Evidence: B)*

5 A noninvasive test (echocardiogram or radionuclide angiogram) is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography. *(Level of Evidence: B)*

Revascularization with PCI and CABG in patients with UA/NSTEMI

a. Percutaneous coronary intervention

Class I

1 An early invasive percutaneous coronary intervention (PCI) strategy is indicated for patients with UA/NSTEMI who have no serious comorbidity and who have coronary lesions amenable to PCI and any high-risk features.

2 Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-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. *(Level of Evidence: 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. *(Level of Evidence: A)*

4 An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients

undergoing PCI. *(Level of Evidence: A)* See Figures 2.8, 2.9, and 2.10 for details on timing and dosing recommendations.

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. *(Level of Evidence: C)*

2 Percutaneous coronary intervention (or CABG) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. *(Level of Evidence: B)*

3 Percutaneous coronary intervention (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. *(Level of Evidence: 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. *(Level of Evidence: 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. *(Level of Evidence: B)*

2 Percutaneous coronary intervention may be considered for UA/NSTEMI patients who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal left anterior descending CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy. *(Level of Evidence: B)*

Class III

1 Percutaneous coronary intervention (or CABG) is not recommended for patients with 1- or 2-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. *(Level of Evidence: 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. *(Level of Evidence: C)*

b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. *(Level of Evidence: C)*

c. A high risk of procedure-related morbidity or mortality. *(Level of Evidence: C)*

d. Insignificant disease (less than 50% coronary stenosis). *(Level of Evidence: C)*

e. Significant left main CAD and candidacy for CABG. *(Level of Evidence: B)*

3 A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated. *(Level of Evidence: B)*

b. CABG

Class I

1 Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with significant left main CAD (greater than 50% stenosis). *(Level of Evidence: A)*

2 Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (LVEF less than 0.50). *(Level of Evidence: A)*

3 Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 2-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (LVEF less than 0.50) or ischemia on noninvasive testing. *(Level of Evidence: A)*

4 Coronary artery bypass graft surgery is recommended for UA/NSTEMI in patients in whom percutaneous revascularization is not optimal or possible and who have ongoing ischemia not responsive to maximal nonsurgical therapy. *(Level of Evidence: B)*

5 Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with 1- or 2-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. *(Level of Evidence: 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. *(Level of Evidence: 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. *(Level of Evidence: B)*

2 It is reasonable to perform CABG with the internal mammary artery for UA/NSTEMI patients with multivessel disease and treated diabetes mellitus. *(Level of Evidence: 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 left anterior descending coronary artery (LAD). *(Level of Evidence: C)*

4 Coronary artery bypass graft surgery (or PCI) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. *(Level of Evidence: B)*

5 Coronary artery bypass graft surgery (or PCI) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. *(Level of Evidence: B)*

6 Coronary artery bypass graft surgery (or PCI with stenting) is reasonable for patients with multivessel disease and symptomatic myocardial ischemia. *(Level of Evidence: B)*

Class IIb

Coronary artery bypass graft surgery may be considered in patients with UA/NSTEMI who have 1- or 2-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.) *(Level of Evidence: B)*

Class III

Coronary artery bypass graft surgery (or PCI) is not recommended for patients with 1- or 2-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. *(Level of Evidence: C)*

Late hospital care, hospital discharge, and post-hospital discharge care

a. Medical regimen and use of medications

Recommendations

Class I

1 All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. *(Level of Evidence: 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. *(Level of Evidence: C)*

b. Long-term medical therapy and secondary prevention

For additional details, see Table 2.3 and full text.

I. Antiplatelet therapy

See Figure 2.9.

Class I

1 For UA/NSTEMI patients treated medically without stenting, aspirin* (75 to 162 mg per day) should be prescribed indefinitely. *(Level of Evidence: A)*; clopidogrel† (75 mg per day) should be

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* For ASA-allergic patients, use clopidogrel alone (indefinitely) or try aspirin desensitization.

† Some uncertainty exists about the optimal loading dose. 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 as well as safety of higher oral loading doses have not been rigorously established.

Table 2.4 Comparison of ESC and ACC/AHA Guideline Recommendations for Anticoagulants

Anticoagulant therapy for an initial invasive strategy	ESC	ACC/AHA
Unfractionated heparin	IC	IA
Enoxaparin	IIa-B	IA
Fondaparinux	Not recommended for urgent invasive; IA (with added heparin, IIa-C) for non-urgent invasive strategy	IB
Bivalirudin	IB	IB
Anticoagulant therapy for an initial conservative strategy		
Unfractionated heparin	IC	IA
Enoxaparin	IIa-B	IA
Fondaparinux	IA	IB

prescribed for al least 1 month *(Level of Evidence: A)* and ideally for up to 1 year *(Level of Evidence: B)*

2 For UA/NSTEMI patients treated with PCI with bare-metal stents, aspirin* 162 to 325 mg per day should be prescribed for at least 1 month *(Level of Evidence: B)*, then continued indefinitely at a dose of 75 to 162 mg per day. *(Level of Evidence: 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). *(Level of Evidence: 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 *(Level of Evidence: B)*, then continued indefinitely at a dose of 75 to 162 mg per day. *(Level of Evidence: A)*. Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES *(Level of Evidence: B)*

4 Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when ASA is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors). *(Level of Evidence: 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. *(Level of Evidence: B)*

2 Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme. *(Level of Evidence: 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. *(Level of Evidence: 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. *(Level of Evidence: 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 radiological signs of HF and LVEF less than 0.40. *(Level of Evidence: 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 per min) or hyperkalemia (potassium should be less than or equal to 5 mEq per 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. *(Level of Evidence: 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. *(Level of Evidence: A)*

2 Angiotensin-converting enzyme inhibitors are reasonable for patients with HF and LVEF greater than 0.40. *(Level of Evidence: 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 radiological signs of HF and LVEF less than 0.40. *(Level of Evidence: B)*

IV. Nitroglycerin

Class I

Nitroglycerin to treat ischemic symptoms is recommended. *(Level of Evidence: C)*

V. Calcium channel blockers

Class I

1 Calcium channel blockers§ are recommended for ischemic symptoms when beta-blockers are not successful. *(Level of Evidence: B)*

2 Calcium channel blockers§ are recommended for ischemic symptoms when beta-blockers are contraindicated or cause unacceptable side effects. *(Level of Evidence: C)*

VI. Lipid management

See also summary in Table 2.3.

Class I

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. *(Level of Evidence: A)*

b. For hospitalized patients, lipid-lowering medications should be initiated before discharge. (*Level of Evidence: 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 *(Level of Evidence: A)*. Further titration to less than 70 mg per dL is reasonable *(Class IIa, Level of Evidence: A)*.

d. Therapeutic options to reduce non-HDL-C are recommended, including more intense LDL-C-lowering therapy *(Level of Evidence: 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 d), and trans fat (to less than 1% of energy). *(Level of Evidence: B)*

f. Promoting daily physical activity and weight management are recommended. *(Level of Evidence: B)*

Class IIb

Encouraging consumption of omega-3 fatty acids in the form of fish¶ or in capsule form (1 g per d) for risk reduction may be reasonable. For treatment of elevated triglycerides, higher doses (2 to 4 g per d) may be used for risk reduction. *(Level of Evidence: 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. *(Level of Evidence: 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% (*Level of Evidence: B*). Diabetes management should also include the following:

a. Vigorous modification of other risk factors (e.g., physical activity, weight management, blood

§ Short-acting dihydropyridine calcium channel blockers should be avoided.

¶ Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

pressure control, and cholesterol management) as recommended should be initiated and maintained. *(Level of Evidence: B)*

b. It is useful to coordinate the patient's diabetic care with the patient's primary care physician or endocrinologist. *(Level of Evidence: 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). (*Level of Evidence: 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 per 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. *(Level of Evidence: B)*

XI. Physical activity

Class I

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. *(Level of Evidence: B)*

XII. Depression

Class IIa

It is reasonable to consider screening UA/NSTEMI patients for depression and refer/treat when indicated. *(Level of Evidence: B)*

b. 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. *(Level of Evidence: B)*

c. Special groups: older adults

Class I

Attention should be given to appropriate dosing (i.e., adjusted by weight and estimated creatinine clearance) of pharmacological agents 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). *(Level of Evidence: B)*

d. Special groups: chronic kidney disease

Class I

Creatinine clearance should be estimated in UA/NSTEMI patients, and the doses of renally cleared drugs should be adjusted appropriately. *(Level of Evidence: B)*

Comparison of ESC with ACC/AHA approach

The European Society of Cardiology (ESC) published updated guidelines nearly simultaneously (June 14, 2007) [19] with the ACC/AHA update (August 18, 2007) [1]. These ESC guidelines form a useful, complementary resource for the diagnosis and treatment of the non-ST-segment elevation acute coronary syndromes. Although independently crafted and distinctive in style, these two guidelines benefited from interval discussions between the chairs and co-chairs of the two writing committees during development and are generally in agreement. A few caveats about the ESC guidelines and comparisons with those of ACC/AHA are appropriate, however. The ESC approach was practical, clinically oriented, and concise (Christian Hamm, MD, personal communication, 31 March 2008): the ESC guidelines comprise 63 pages and 574 references, much shorter than the 159 pages and 957 references in the full ACC/AHA guidelines and, indeed, shorter than the ACC/AHA executive summary (78 pages, 370 references). Other factors being equal, contemporary, blinded, and large studies received higher levels of evidence in the ESC guidelines than older, unblinded, or smaller studies, distinctions not as clearly made in the ACC/AHA version. Also, relative bleeding risks were carefully considered. As a result, some differences in levels of evidence and a few for class recommendations occur, with the ESC guidelines being more distinctive and prescriptive, e.g.,

for anticoagulant agents (Table 2.4). ESC downgrades evidence for unfractionated heparin to IB (older studies), upgrades evidence for fondaparinux for a conservative approach (to IA), based on the single large and blinded OASIS-5 study [15], but limits its recommendations with an invasive approach because of catheter thrombosis risk (not recommended with an urgent invasive approach; give with heparin for a non-urgent invasive approach). ESC also downgrades enoxaparin (to IIaB), given the superior safety of fondaparinux in OASIS-5 [15]. Bivalirudin also receives a IB recommendation by ESC for an invasive approach but for a different reason: the key supporting study, ACUITY, although large, was unblinded [16]. ESC more explicitly endorses GP IIb/IIIa therapy in patients at intermediate to high risk *in addition* to oral antiplatelet agents (e.g., clopidogrel and aspirin), especially with elevated troponins, ST-segment depression, or diabetes [20]. ESC, as ACC/AHA, generally favors an invasive approach for high risk patients, but adds diabetes, renal insufficiency, and intermediate risk (in addition to high risk) more explicitly to indications favoring invasive evaluation, which may occur within 72 hours (versus 24–48 in the ACC/AHA guidelines).

Future directions

Whereas the incidence and risk of STEMI have decreased over the past 25 years, the relative frequency of UA/NSTEMI has increased. The early risk of UA/NSTEMI has decreased with application of evidence-based management [21], but risk remains relatively high long-term (i.e., comparable to STEMI). Hence, improving long-term UA/NSTEMI outcomes remains a challenge for the future.

Improving prehospital and ED assessment should aim at more efficient entry into the healthcare system, diagnosis and risk stratification (e.g., using biomarker changes still in the normal range but rising and with the aid of non-traditional biomarkers) and earlier initiation of therapy. The future likely will witness increased use of new imaging tests such as multislice coronary CT angiography, especially if radiation risks are further reduced, and cardiac MRI to assess chest pain patients with possible ACS [2]. The concept of a network of "heart attack centers" has been proposed to improve MI care in the future, with evidence favoring interventions at experienced centers and at earlier time intervals [22]. However, the preferred strategy (initial invasive vs. initial conservative) and timing of invasive evaluation for subsets of patients with UA/NSTEMI continues to be debated and is an appropriate topic for ongoing (e.g., TIMACS) and future research studies. In contrast to evidence of benefit of invasive strategies for high-risk patients, growing evidence suggests that an initial conservative approach is preferred for patients at low risk of UA/NSTEMI, particularly low-risk women [7–9].

Antiplatelet therapy continues to evolve, with higher dose clopidogrel and new thienopyridines (e.g., prasugrel [23]) being tested, including short acting, intravenously administered agents [24]. The future may include greater application of platelet function analyzers to titrate therapeutic dosing to individual patient needs. Anticoagulant choices have proliferated (e.g., with the addition of fondaparinux [15] and bivalirudin [16] to unfractionated and low molecular weight heparins), and continued evolution in their application in UA/NSTEMI can be expected with the goal of maximum benefit at lowest bleeding risk. Greater emphasis and application is needed in adjusting dose for renal function, older age, and female sex with these increasingly potent antithrombotic regimens to preserve safety and improve overall clinical benefit [17]. Testing of more biocompatible stents, less prone to thrombosis and restenosis, also can be expected, including biodegradable stents [25].

Greater and more effective application of secondary prevention including cardiac rehabilitation should benefit UA/NSTEMI and all CHD patients in the future [18], guided by trials of lifestyle, pharmaceutical, and surgical interventions. Finally, more effective primary prevention strategies, including better identification of the "ACS-prone" individual are anticipated, including life-time risk assessment and selected application of imaging tests (e.g., with coronary calcium scans or carotid intima-media thickness assessment) to detect preclinical disease [26,27]. Predictive medicine thus is an important feature on the future horizon of UA/NSTEMI and the full spectrum of atherothrombotic disease.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

3 ST-Elevation Myocardial Infarction

Elliott M. Antman

Recommendations for management of patients with STEMI
Management before STEMI
A. Identification of patients at risk of STEMI
B. Patient education for early recognition and response to STEMI
Onset of STEMI
A. Out-of-hospital cardiac arrest
Prehospital issues
A. Emergency medical services systems
B. Prehospital chest pain evaluation and treatment
C. Prehospital fibrinolysis
D. Prehospital destination protocols
Initial recognition and management in the Emergency Department
A. Optimal strategies for Emergency Department triage
B. Initial patient evaluation
1. History
2. Physical examination
3. Electrocardiogram
4. Laboratory examinations
5. Biomarkers of cardiac damage
6. Imaging
C. Management
1. Routine measures
Hospital management
A. Location
1. Coronary care unit
2. Stepdown unit
B. Early, general measures
1. Level of activity
2. Diet
3. Patient education in the hospital setting
4. Analgesia/anxiolytics
C. Medication assessment
1. Beta-blockers
2. Nitroglycerin
3. Inhibition of the rennin–angiotensin–aldosterone system
4. Antiplatelets
5. Anticoagulents
6. Oxygen
D. Estimation of infarct size
1. Electrocardiographic techniques
E. Hemodynamic disturbances
1. Hemodynamic assessment
2. Hypotension
3. Low-output state
4. Pulmonary congestion
5. Cardiogenic shock
6. Right ventricular infarction
7. Mechanical causes of heart failure/low-output syndrome
F. Arrhythmias after STEMI
1. Ventricular arrhythmias
2. Supraventricular arrhythmias/atrial fibrillation
3. Bradyarrhythmias
G. Recurrent chest pain after STEMI
1. Pericarditis
2. Recurrent ischemia/infarction
H. Other complications
1. Ischemic stroke
2. DVT and pulmonary embolism
I. CABG surgery after STEMI
1. Timing of surgery
2. Arterial grafting
3. CABG for recurrent ischemia after STEMI
4. Elective CABG surgery after STEMI in patients with angina
5. CABG surgery after STEMI and antiplatelet agents

The AHA Guidelines and Scientific Statements Handbook
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J. Convalescence, discharge, and post-MI care
1. Risk stratification at hospital discharge
K. Secondary prevention
1. Patient education before discharge
2. Antiplatelet therapy
Long-term management
A. Psychosocial impact of STEMI
B. Cardiac rehabilitation
C. Follow-up visit with medical provider
Comparison with ESC STEMI Guidelines
Ongoing research efforts and future directions

Recommendations for management of patients with STEMI

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format and arranged along the chronology of the interface of the clinician and a patient with STEMI (Figures 3.1–3.3) [1,2].

Management before STEMI

A. Identification of patients at risk of STEMI

Class I

1 Primary care providers should evaluate the presence and status of control of major risk factors for

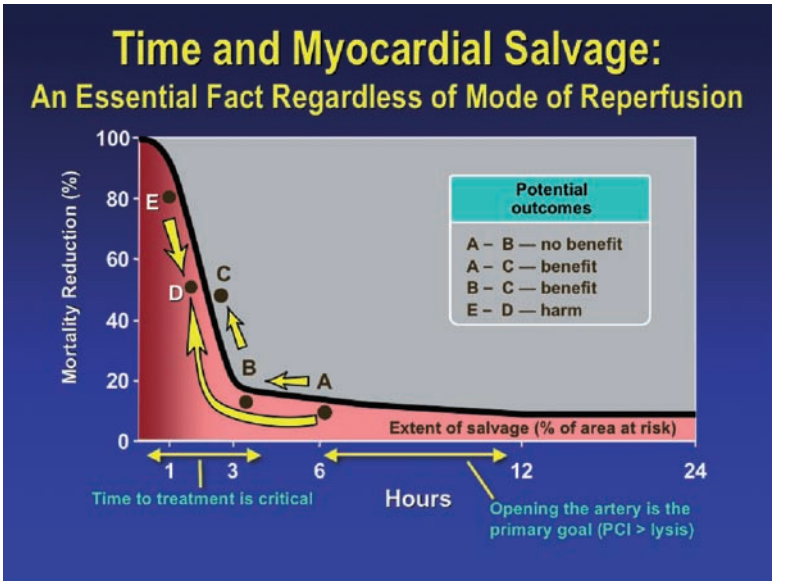


Fig. 3.1 Hypothetical construct of the relationship among the duration of symptoms of acute MI before reperfusion therapy, mortality reduction, and extent of myocardial salvage. Mortality reduction as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute myocardial infarction (MI), most likely a consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. If a treatment strategy, such as facilitated percutaneous coronary intervention (PCI), is able to move patients back up the curve, a benefit would be expected. The magnitude of the benefit will depend on how far up the curve the patient can be shifted. The benefit of a shift from points A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. A treatment strategy that delays therapy during the early critical period, such as patient transfer for PCI, would be harmful (shift from point D to point C or point B). Between 6 and 12 hours after the onset of symptoms, opening the infarct-related artery is the primary goal of reperfusion therapy, and primary PCI is preferred over fibrinolytic therapy. The possible contribution to mortality reduction of opening the infarct-related artery, independent of myocardial salvage, is not shown. Modified from Gersh and Anderson (Circulation. 1993;88:296–306). Reproduced from JAMA. 2005;293:979.

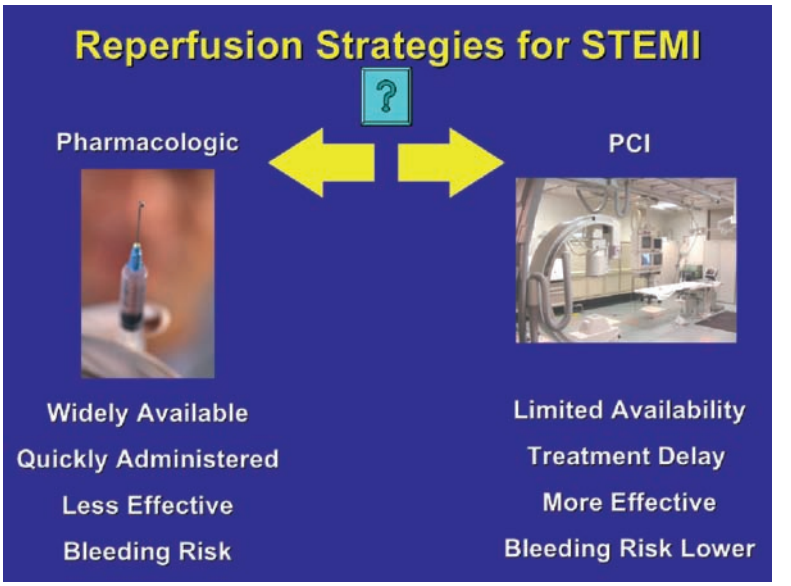


Fig. 3.2 Comparison of major features of reperfusion strategy for STEMI. PCI, percutaneous coronary intervention. Modified from Libby *et al.* (eds.) Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia, PA: Saunders, 2008, p. 1284.

coronary heart disease (CHD) for all patients at regular intervals (approximately every 3 to 5 years). *(Level of Evidence: C)* [3,4]

2 Ten-year risk (National Cholesterol Education Program [NCEP] global risk) of developing symptomatic CHD should be calculated for all patients who have two or more major risk factors to assess the need for primary prevention strategies. *(Level of Evidence: B)*

3 Patients with established CHD should be identified for secondary prevention, and patients with a CHD risk equivalent (e.g., diabetes mellitus, chronic kidney disease, or 10-year risk greater than 20% as calculated by Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD. *(Level of Evidence: A)*

B. Patient education for early recognition and response to STEMI [5,6]

Class I

1 Patients with symptoms of STEMI (chest discomfort with or without radiation to the arms[s], back, neck, jaw, or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be transported to the hospital by ambulance rather than by friends or relatives. *(Level of Evidence: B)*

2 Healthcare providers should actively address the following issues regarding STEMI with patients and their families: (a) the patient's heart attack risk *(Level of Evidence: C)*; (b) how to recognize symptoms of STEMI *(Level of Evidence: C)*; (c) the advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 minutes, despite feelings of uncertainty about the symptoms and fear of potential embarrassment *(Level of Evidence: C)*; (d) a plan for appropriate recognition and response to a potential acute cardiac event that includes the phone number to access emergency medical services (EMS), generally 9-1-1. *(Level of Evidence: C)*

3 Healthcare providers should instruct patients for whom nitroglycerin has been prescribed previously to take ONE nitroglycerin dose sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or worsening 5 minutes after one sublingual nitroglycerin dose has been taken, it is recommended that the patient or family member/friend call 9-1-1 immediately to access EMS. *(Level of Evidence: C)*

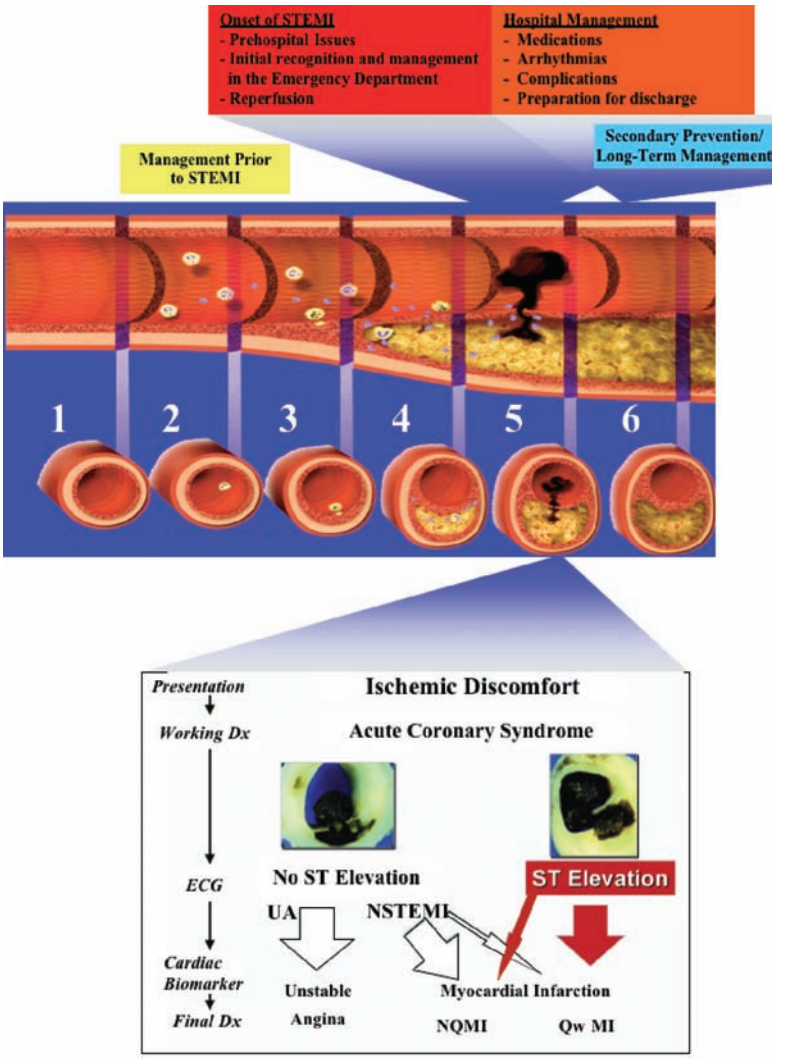


Fig. 3.3 Acute coronary syndromes. The top half of the figure illustrates the chronology of the interface between the patient and the clinician through the progression of plaque formation, onset and complications of STEMI along with relevant management considerations at each stage. The longitudinal section of an artery depicts the "timeline" of atherogenesis from a normal artery (1) to (2) lesion initiation and accumulation of extracellular lipid in the intima; to (3) the evolution to the fibrofatty stage; to (4) lesion progression with procoagulant expression and weakening of the fibrous cap. An acute coronary syndrome 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 or high-risk 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 side) or subtotally occlusive thrombus (bottom half, left side). Patients with ischemic discomfort may present with or without ST segment elevation on the ECG. Of patients with ST segment elevation, most (large red arrow in bottom panel) ultimately develop a Q-wave MI (QwMI), while a few (small red arrow) develop a non-Q-wave MI (NQMI). Patients who present without ST segment elevation are suffering from either unstable angina or a non-ST segment elevation MI (NSTEMI) (large open arrows), a distinction that is ultimately made on the presence or absence of a serum cardiac marker such as CKMB or a cardiac troponin detected in the blood. Most patients presenting with NSTEMI ultimately develop a NQMI on the ECG; a few may develop a QwMI. The spectrum of clinical presentations ranging from unstable angina through NSTEMI and STEMI are referred to as the acute coronary syndromes.

This STEMI guideline is arranged along the chronologic interface of the clinician with the patient, as diagrammed in the upper panel, and includes sections on management prior to STEMI, at the onset of STEMI, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase of treatment.

Dx, diagnosis; NQMI, non-Q-wave myocardial infarction; QwMI, Q-wave myocardial infarction. Modified from Libby P. Circulation 2001;104:365; Hamm CW, Bertrand M, Braunwald E. Lancet. 2001;358:1533–8 and Davies MJ. Heart. 2000;83:361–6.

Onset of STEMI

A. Out-of-hospital cardiac arrest

Class I

1 All communities should create and maintain a strong "Chain of Survival" for out-of-hospital cardiac arrest that includes early access (recognition of the problem and activation of the EMS system by a bystander), early cardiopulmonary resuscitation (CPR), early defibrillation for patients who need it, and early advanced cardiac life support (ACLS). *(Level of Evidence: C)*

2 Family members of patients experiencing STEMI should be advised to take CPR training and familiarize themselves with the use of an automated external defibrillator (AED). In addition, they should be referred to a CPR training program that has a social support component for family members of post-STEMI patients. *(Level of Evidence: B)*

Prehospital issues

See Figure 3.4.

A. Emergency medical services systems

Class I

1 All EMS first responders who respond to patients with chest pain and/or suspected cardiac arrest should be trained and equipped to provide early defibrillation. *(Level of Evidence: A)*

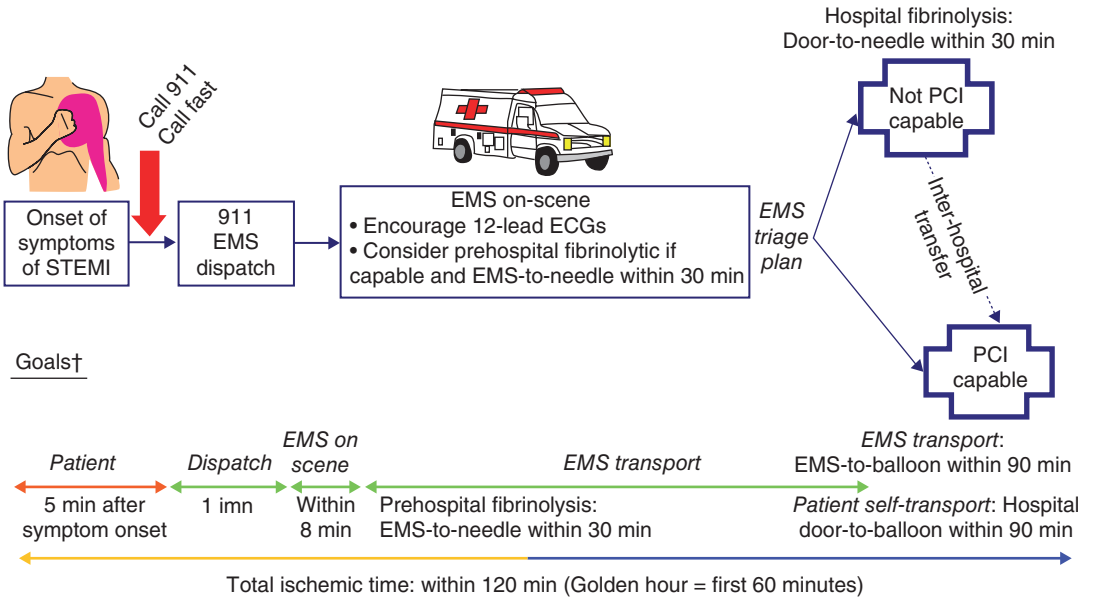
2 All public safety first responders who respond to patients with chest pain and/or suspected cardiac arrest should be trained and equipped to provide early defibrillation with AEDs. (Provision of early defibrillation with AEDs by nonpublic safety first responders is a promising new strategy, but further study is needed to determine its safety and efficacy.) *(Level of Evidence: B)*

3 Dispatchers staffing 9-1-1 center emergency medical calls should have medical training, should use nationally developed and maintained protocols, and should have a quality-improvement system in place to ensure compliance with protocols. *(Level of Evidence: C)*

B. Prehospital chest pain evaluation and treatment

Class I

Prehospital EMS providers should administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having STEMI unless contraindicated or already taken by patient. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. *(Level of Evidence: C)*



Class IIa

1 It is reasonable for all 9-1-1 dispatchers to advise patients without a history of aspirin allergy who have symptoms of STEMI to chew aspirin (162 to 325 mg) while awaiting arrival of prehospital EMS providers. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. *(Level of Evidence: C)*

2 It is reasonable that all ACLS providers perform and evaluate 12-lead electrocardiograms (ECGs) routinely on chest pain patients suspected of STEMI. *(Level of Evidence: B)* [7–9]

3 If the ECG shows evidence of STEMI, it is reasonable that prehospital ACLS providers review a reperfusion "checklist" and relay the ECG and checklist findings to a predetermined medical control facility and/or receiving hospital. *(Level of Evidence: C)*

Fig. 3.4 Options for transportation of STEMI patients and initial reperfusion treatment goals. Reperfusion in patients with STEMI can be accomplished by pharmacological (fibrinolysis) or catheter-based (primary PCI) approaches. The overarching goal is to *keep total ischemic time within 120 minutes* (ideally within 60 minutes) from symptom onset to initiation of reperfusion treatment. Within this context, the following are goals for the medical system* based on the mode of patient transportation and the capabilities of the receiving hospital:

Medical system goals: EMS transport (recommended):

- If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 minutes of arrival of EMS on the scene.
- If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a *non*-PCI-capable hospital, the *door-to-needle* time should be within 30 minutes or patients for whom fibrinolysis is indicated.
- If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the *EMS arrival-to-balloon* time should be within 90 minutes.
- If EMS takes the patient to a *non*-PCI-capable hospital, it is appropriate to consider emergency *interhospital transfer* of the patient to a PCI-capable hospital for mechanical revascularization if:
  - There is a contraindication to fibrinolysis.
  - PCI can be initiated promptly within 90 minutes *from EMS arrival-to-balloon time at the PCI-capable hospital.*†
  - Fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI").

Patient self-transport (discouraged):

- If the patient arrives at a non-PCI-capable hospital, the *door-to-needle* time should be within 30 minutes of arrival at the emergency department.
- If the patient arrives at a PCI-capable hospital, the *door-to-balloon* time should be within 90 minutes.
- If the patient presents to a non-PCI-capable hospital, it is appropriate to consider emergency *interhospital transfer* of the patient to a PCI-capable hospital if:
  - There is a contraindication to fibrinolysis.
  - PCI can be initiated within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared with when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital.
  - Fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI").

*The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI so that *door-to-needle* (or *medical contact-to-needle*) for initiation of fibrinolytic therapy can be achieved within 30 minutes or *door-to-balloon* (or *medical contact-to-balloon*) for PCI can be achieved within 90 minutes. These goals should not be understood as "ideal" times but rather the longest times that should be considered acceptable for a given system. Systems that are able to achieve even more rapid times for treatment of patients with STEMI should be encouraged. Note "*medical contact*" is defined as "time of EMS arrival on scene" after the patient calls EMS/9-1-1 or "time of arrival at the emergency department door" (whether PCI-capable or non-PCI-capable hospital) when the patient transports himself/herself to the hospital.

†EMS Arrival→Transport to non-PCI-capable hospital→Arrival at non-PCI-capable hospital to transfer to PCI-capable hospital→Arrival at PCI-capable *hospital-to-balloon* time = 90 minutes.

EMS indicates emergency medical services; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Modified from Armstrong *et al.* Circulation. 2003;107:2533–7.

C. Prehospital fibrinolysis

See Figure 3.4.

Class IIa

Establishment of a prehospital fibrinolysis protocol is reasonable in (1) settings in which physicians are present in the ambulance or in (2) well-organized EMS systems with full-time paramedics who have 12-lead ECGs in the field with transmission capability, paramedic initial and ongoing training in ECG interpretation and STEMI treatment, online medical command, a medical director with training/experience in STEMI management, and an ongoing continuous quality-improvement program. *(Level of Evidence: B)* [10]

D. Prehospital destination protocols

See Figure 3.4 [11].

Class I

1 Patients with STEMI who have cardiogenic shock and are less than 75 years of age should be brought immediately or secondarily transferred to facilities capable of cardiac catheterization and rapid revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) if it can be performed within 18 hours of onset of shock. *(Level of Evidence: A)*

2 Patients with STEMI who have contraindications to fibrinolytic therapy should be brought immediately or secondarily transferred promptly (i.e., primary receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). *(Level of Evidence: B)*

3 Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed STEMI. *(Level of Evidence: C)*

Class IIa

1 It is reasonable that patients with STEMI who have cardiogenic shock and are 75 years of age or older be considered for immediate or prompt secondary transfer to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG) if it can be performed within 18 hours of onset of shock. *(Level of Evidence: B)*

2 It is reasonable that patients with STEMI who are at especially high risk of dying, including those with severe congestive heart failure (CHF), be considered for immediate or prompt secondary transfer (i.e., primary-receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). *(Level of Evidence: B)*

Initial recognition and management in the Emergency Department

See Figure 3.4.

A. Optimal strategies for Emergency Department triage

Class I

Hospitals should establish multidisciplinary teams (including primary care physicians, emergency medicine physicians, cardiologists, nurses, and laboratorians) to develop guideline-based, institution-specific written protocols for triaging and managing patients who are seen in the prehospital setting or present to the emergency department (ED) with symptoms suggestive of STEMI. *(Level of Evidence: B)*

B. Initial patient evaluation

Class I

1 The delay from patient contact with the healthcare system (typically, arrival at the ED or contact with paramedics) to initiation of fibrinolytic therapy should be less than 30 minutes. Alternatively, if PCI is chosen, the delay from patient contact with the healthcare system (typically, arrival at the ED or contact with paramedics) to balloon inflation should be less than 90 minutes. *(Level of Evidence: B)*

2 The choice of initial STEMI treatment should be made by the emergency medicine physician on duty based on a predetermined, institution-specific, written protocol that is a collaborative effort of cardiologists (both those involved in coronary care unit management and interventionalists), emergency physicians, primary care physicians, nurses, and other appropriate personnel. For cases in which the initial diagnosis and treatment plan is unclear to the emergency physician or is not covered directly by the agreed-on protocol, immediate cardiology consultation is advisable. *(Level of Evidence: C)*

1. History

Class I

The targeted history of STEMI patients taken in the ED should ascertain whether the patient has had prior episodes of myocardial ischemia such as stable or unstable

Table 3.1 Brief physical examination in the Émergency Department

1. Airway, Breathing, Circulation (ABC)
2. Vital signs, general observation
3. Presence or absence of jugular venous distension
4. Pulmonary auscultation for rales
5. Cardiac auscultation for murmurs and gallops
6. Presence or absence of stroke
7. Presence or absence of pulses
8. Presence or absence of systemic hypoperfusion (cool, clammy, pale, ashen)

angina, MI, CABG, or PCI. Evaluation of the patient's complaints should focus on chest discomfort, associated symptoms, sex- and age-related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia, or vertigo). *(Level of Evidence: C)*

2. Physical examination (Table 3.1)

Class I

1 A physical examination should be performed to aid in the diagnosis and assessment of the extent, location, and presence of complications of STEMI. *(Level of Evidence: C)*

2 A brief, focused, and limited neurological examination to look for evidence of prior stroke or cognitive deficits should be performed on STEMI patients before administration of fibrinolytic therapy. *(Level of Evidence: C)*

3. Electrocardiogram

Class I

1 A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 minutes of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of STEMI. *(Level of Evidence: C)*

2 If the initial ECG is not diagnostic of STEMI but the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST elevation. *(Level of Evidence: C)*

3 In patients with inferior STEMI, right-sided ECG leads should be obtained to screen for ST elevation suggestive of right ventricular (RV) infarction. (See Section 7.6.6 of the full-text guidelines and the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography.) *(Level of Evidence: B)*

4. Laboratory examinations

Class I

Laboratory examinations should be performed as part of the management of STEMI patients but should not delay the implementation of reperfusion therapy. *(Level of Evidence: C)*

5. Biomarkers of cardiac damage

Class I

1 Cardiac-specific troponins should be used as the optimum biomarkers for the evaluation of patients with STEMI who have coexistent skeletal muscle injury. *(Level of Evidence: C)*

2 For patients with ST elevation on the 12-lead ECG and symptoms of STEMI, reperfusion therapy should be initiated as soon as possible and is not contingent on a biomarker assay. *(Level of Evidence: C)*

Class IIa

Serial biomarker measurements can be useful to provide supportive noninvasive evidence of reperfusion of the infarct artery after fibrinolytic therapy in patients not undergoing angiography within the first 24 hours after fibrinolytic therapy. *(Level of Evidence: B)*

Class III

Serial biomarker measurements should not be relied on to diagnose reinfarction within the first 18 hours after the onset of STEMI. *(Level of Evidence: C)*

a. Bedside testing for serum cardiac biomarkers

Class I

1 Although handheld bedside (point-of-care) assays may be used for a qualitative assessment of the presence of an elevated level of a serum cardiac biomarker, subsequent measurements of cardiac biomarker levels should be performed with a quantitative test. *(Level of Evidence: B)*

2 For patients with ST elevation on the 12-lead ECG and symptoms of STEMI, reperfusion therapy

should be initiated as soon as possible and is not contingent on a bedside biomarker assay. *(Level of Evidence: C)*

6. Imaging

Class I

1 Patients with STEMI should have a portable chest X-ray, but this should not delay implementation of reperfusion therapy (unless a potential contraindication, such as aortic dissection, is suspected). *(Level of Evidence: C)*

2 Imaging studies such as a high-quality portable chest X-ray, transthoracic and/or transesophageal echocardiography, and a contrast chest computed tomographic scan or a MRI scan should be used to differentiate STEMI from aortic dissection in patients for whom this distinction is initially unclear. *(Level of Evidence: B)*

Class IIa

Portable echocardiography is reasonable to clarify the diagnosis of STEMI and allow risk stratification of patients with chest pain on arrival at the ED, especially if the diagnosis of STEMI is confounded by left bundle branch block (LBBB) or pacing, or there is suspicion of posterior STEMI with anterior ST depressions. (See Section 7.6.7 Mechanical Causes of Heart Failure/Low Output Syndrome of the full-text guidelines.) *(Level of Evidence: B)*

Class III

Single-photon emission computed tomography (SPECT) radionuclide imaging should not be performed to diagnose STEMI in patients for whom the diagnosis of STEMI is evident on the ECG. *(Level of Evidence: B)*

C. Management

1. Routine measures

a. Oxygen

Class I

Supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO_2 less than 90%). *(Level of Evidence: B)*

Class IIa

It is reasonable to administer supplemental oxygen to all patients with uncomplicated STEMI during the first 6 hours. *(Level of Evidence: C)*

b. Nitroglycerin

Class I

1 Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses, after which an assessment should be made about the need for intravenous nitroglycerin. *(Level of Evidence: C)*

2 Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. *(Level of Evidence: C)*

Class III

1 Nitrates should not be administered to 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 bpm), tachycardia (more than 100 bpm), or suspected RV infarction. *(Level of Evidence: C)*

2 Nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (48 hours for tadalafil). *(Level of Evidence: B)*

c. Analgesia

Class I

1 Morphine sulfate (2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. (*Level of Evidence: C)*

2 Patients routinely taking NSAIDs (except for aspirin), both nonselective as well as COX-2 selective agents, before STEMI should have those agents discontinued at the time of presentation with STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use. *(Level of Evidence: C)*

Class III

NSAIDs (except for aspirin), both nonselective as well as COX-2 selective agents, should not be administered during hospitalization for STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use. *(Level of Evidence: C)*

d. Aspirin

Class I

Aspirin should be chewed by patients who have not taken aspirin before presentation with STEMI. The

initial dose should be 162 mg *(Level of Evidence: A)* to 325 mg *(Level of Evidence: C)*. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated aspirin formulations.

e. Beta-blockers [2]

Class I

1 Oral beta-blocker therapy should be initiated in the first 24 hours for patients who do not have any of the following: (1) signs of heart failure; (2) evidence of a low output state; (3) increased risk* for cardiogenic shock; or (4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). *(Level of Evidence: B)*

2 Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for beta-blocker therapy as secondary prevention. *(Level of Evidence: C)*

3 Patients with moderate or severe LV failure should receive beta-blocker therapy as secondary prevention with a gradual titration scheme. *(Level of Evidence: B)*

Class IIa

It is reasonable to administer an intravenous beta blocker at the time of presentation to STEMI patients who are hypertensive and who do not have any of the following: (1) signs of heart failure; (2) evidence of a low output state; (3) increased risk* for cardiogenic shock; or (4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second or third degree heart block, active asthma or reactive airway disease). *(Level of Evidence: B)*

Class III

Intravenous beta-blockers should not be administered to STEMI patients who have any of the following: (1) signs of heart failure; (2) evidence of a low output state; (3) increased risk* for cardiogenic shock; or (4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second or third degree heart block, active asthma or reactive airway disease). *(Level of Evidence: A)*

f. Reperfusion

General concepts

See Table 3.2 for selection of reperfusion therapy.

Class I

1 STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact (see Figure 3.4) as a systems goal. *(Level of Evidence: A)*

2 STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact (see Figure 3.1) should be treated with fibrinolytic therapy within 30 minutes of hospital presentation as a systems goal unless fibrinolytic therapy is contraindicated. *(Level of Evidence: B)*

Pharmacological reperfusion

See Figure 3.4 [12,13].

Indications for fibrinolytic therapy

Class I

1 In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least two contiguous precordial leads or at least 2 adjacent limb leads. *(Level of Evidence: A)*

2 In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB. *(Level of Evidence: A)*

Class IIa

1 In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12

* Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age greater than 70 years, systolic blood pressure less than 120 mm Hg, sinus tachycardia greater than 110 bpm or heart rate less than 60 bpm, and increased time since onset of symptoms of STEMI. IV indicates intravenous; LOE, level of evidence; LV, left ventricular; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Table 3.2 Assessment of reperfusion options for STEMI patients

STEP 1: Assess time and risk

- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time required for transport to a skilled PCI lab

STEP 2: Determine if fibrinolysis or an invasive strategy is preferred

- ***If presentation is less than 3 hours and there is no delay to an invasive strategy, there is no preference of either strategy***

Fibrinolysis is generally preferred if

- *Early presentation (less than or equal to 3 hours from symptom onset and delay to invasive strategy) (see below)*
- *Invasive strategy is not an option*
  Catheterization lab occupied/not available
  Vascular access difficulties
  Lack of access to a skilled PCI lab ††
- *Delay to invasive strategy*
  Prolonged transport
  (Door-to-Balloon) – (Door-to-Needle) is greater than 1 hour*§
  Medical Contact-to-Balloon or Door-to-Balloon is greater than 90 minutes

An invasive strategy is generally preferred if

- *Skilled PCI lab available with surgical backup*
  A skilled PCI lab is available, defined by: ††
  Medical Contact-to-Balloon or Door-to-Balloon is less than 90 minutes
  (Door-to-Balloon) – (Door-to-Needle) is less than 1 hour*
- *High risk from STEMI*
  Cardiogenic shock
  Killip class is greater than or equal to 3
- *Contraindications to fibrinolysis including increased risk of bleeding and ICH*
- *Late presentation*
  The symptom onset was greater than 3 hours ago
- *Diagnosis of STEMI is in doubt*

ICH, Intracranial hemorrhage.

* Applies to fibrin-specific agents.

† Operator experience greater than a total of 75 Primary PCI cases/year.

‡ Team experience greater than a total of 36 Primary PCI cases/year.

§ This calculation implies that the estimated delay to the implementation of the invasive strategy is greater than one hour versus initiation of fibrinolytic therapy immediately with a fibrin-specific agent.

hours and 12-lead ECG findings consistent with a true posterior MI. *(Level of Evidence: C)*

2 In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 to 24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least two contiguous precordial leads or at least two adjacent limb leads. *(Level of Evidence: B)*

Class III

1 Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier. *(Level of Evidence: C)*

2 Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression except if a true posterior MI is suspected. *(Level of Evidence: A)*

Contraindications/cautions

Class I

1 Healthcare providers should ascertain whether the patient has neurological contraindications to fibrinolytic therapy, including any history of intracranial hemorrhage (ICH), significant closed head

or facial trauma within the past 3 months, uncontrolled hypertension, or ischemic stroke within the past 3 months. (See Table 3.2 for a comprehensive list.) *(Level of Evidence: A)*

2 STEMI patients at substantial (greater than or equal to 4%) risk of ICH should be treated with PCI rather than with fibrinolytic therapy. (See Figure 3.3 for further management considerations.) *(Level of Evidence: A)*

Complications of fibrinolytic therapy: neurological and other

Class I

1 The occurrence of a change in neurological status during or after reperfusion therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to ICH until proven otherwise. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of ICH. *(Level of Evidence: A)*

2 Neurology and/or neurosurgery or hematology consultations should be obtained for STEMI patients who have ICH as dictated by clinical circumstances. *(Level of Evidence: C)*

3 In patients with ICH, infusions of cryoprecipitate, fresh frozen plasma, protamine, and platelets should be given, as dictated by clinical circumstances. *(Level of Evidence: C)*

Class IIa

In patients with ICH, it is reasonable to:

a. Optimize blood pressure and blood glucose levels. *(Level of Evidence: C)*
b. Reduce intracranial pressure with an infusion of mannitol, endotracheal intubation, and hyperventilation. *(Level of Evidence: C)*
c. Consider neurosurgical evacuation of ICH. *(Level of Evidence: C)*

Class IIb

1 Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction *(Level of Evidence: A)* and other complications of STEMI in selected patients: anterior location of MI, age less than 75 years, and no risk factors for bleeding. In two clinical trials of combination reperfusion, the prevention of reinfarction did not translate into a survival benefit at either 30 days or 1 year. *(Level of Evidence: B)*

2 Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction and other complications of STEMI in selected patients (anterior location of MI, age less than 75 years, and no risk factors for bleeding) in whom an early referral for angiography and PCI (i.e., facilitated PCI) is planned. *(Level of Evidence: C)*

Class III

Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase should not be given to patients aged greater than 75 years because of an increased risk of ICH. *(Level of Evidence: B)*

Percutaneous coronary intervention

See Figure 3.4 [2,12].

Coronary angiography

Class I

Diagnostic coronary angiography should be performed:

a. In candidates for primary or rescue PCI. *(Level of Evidence: A)*
b. In patients with cardiogenic shock who are candidates for revascularization. *(Level of Evidence: A)*
c. In candidates for surgical repair of ventricular septal rupture or severe mitral regurgitation (MR). *(Level of Evidence: B)*
d. In patients with persistent hemodynamic and/or electrical instability. *(Level of Evidence: C)*

Class III

Coronary angiography should not be performed in patients with extensive comorbidities in whom the risks of revascularization are likely to outweigh the benefits. *(Level of Evidence: C)*

Primary PCI See Figure 3.4.

Class I

1 General considerations: If immediately available, primary PCI should be performed in patients with

STEMI (including true posterior MI) or MI with new or presumably new LBBB who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (individuals who perform more than 75 PCI procedures per year). The procedure should be supported by experienced personnel in an appropriate laboratory environment (performs more than 200 PCI procedures per year, of which at least 36 are primary PCI for STEMI, and has cardiac surgery capability). *(Level of Evidence: A)*

2 Specific considerations:

a. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact (see Figure 3.4) as a systems goal. *(Level of Evidence: A)*

b. If the symptom duration is within 3 hours and the expected door-to-balloon time minus the expected door-to-needle time is:

(i) within 1 hour, primary PCI is generally preferred. *(Level of Evidence: B)*

(ii) greater than 1 hour, fibrinolytic therapy (fibrin-specific agents) is generally preferred. *(Level of Evidence: B)*

c. If symptom duration is greater than 3 hours, primary PCI is generally preferred and should be performed with a medical contact-to-balloon or door-to-balloon time as brief as possible, with a goal of within 90 minutes. *(Level of Evidence: B)*

d. Primary PCI should be performed for patients younger than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*

e. Primary PCI should be performed in patients with severe CHF and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. The medical contact–to-balloon or door-to-balloon time should be as short as possible (i.e., goal within 90 min). *(Level of Evidence: B)*

Class IIa

1 Primary PCI is reasonable for selected patients 75 years or older with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

2 It is reasonable to perform primary PCI for patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:

a. Severe CHF *(Level of Evidence: C)*

b. Hemodynamic or electrical instability *(Level of Evidence: C)*

c. Persistent ischemic symptoms. *(Level of Evidence: C)*

Class IIb

The benefit of primary PCI for STEMI patients eligible for fibrinolysis is not well established when performed by an operator who performs fewer than 75 PCI procedures per year. *(Level of Evidence: C)*

Class III

1 PCI should not be performed in a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise. *(Level of Evidence: C)*

2 Primary PCI should not be performed in asymptomatic patients more than 12 hours after onset of STEMI if they are hemodynamically and electrically stable. *(Level of Evidence: C)*

Primary PCI in fibrinolytic-ineligible patients

Class I

Primary PCI should be performed in fibrinolytic ineligible patients who present with STEMI within 12 hours of symptom onset. *(Level of Evidence: C)*

Class IIa

It is reasonable to perform primary PCI for fibrinolytic-ineligible patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:

a. Severe CHF *(Level of Evidence: C)*

b. Hemodynamic or electrical instability *(Level of Evidence: C)*

c. Persistent ischemic symptoms. *(Level of Evidence: C)*

Primary PCI without on-site cardiac surgery

Class IIb

Primary PCI might be considered in hospitals without on-site cardiac surgery, provided that there exists a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with STEMI or MI with new, or presumably new, LBBB on ECG, and should be done in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals that perform a minimum of 36 primary PCI procedures per year. *(Level of Evidence: B)*

Class III

Primary PCI should not be performed in hospitals without on-site cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. *(Level of Evidence: C)*

Facilitated PCI

See Figure 3.5 [14].

Class IIb

Facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered as a reperfusion strategy when all of the following are present: (a) patients are at high risk; (b) PCI is not immediately available within 90 minutes; and (c) bleeding risk is low (younger age, absence of poorly controlled hypertension, normal body weight). *(Level of Evidence: C)*

Class III

A planned reperfusion strategy using full-dose fibrinolytic therapy followed by PCI is not recommended and may be harmful. *(Level of Evidence: B)*

Immediate (or emergency) invasive strategy and rescue PCI See Table 3.3 [15].

Class I

A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is recommended for patients who have received fibrinolytic therapy and have any of the following: (a) cardiogenic shock and age less than 75 years and are suitable candidates

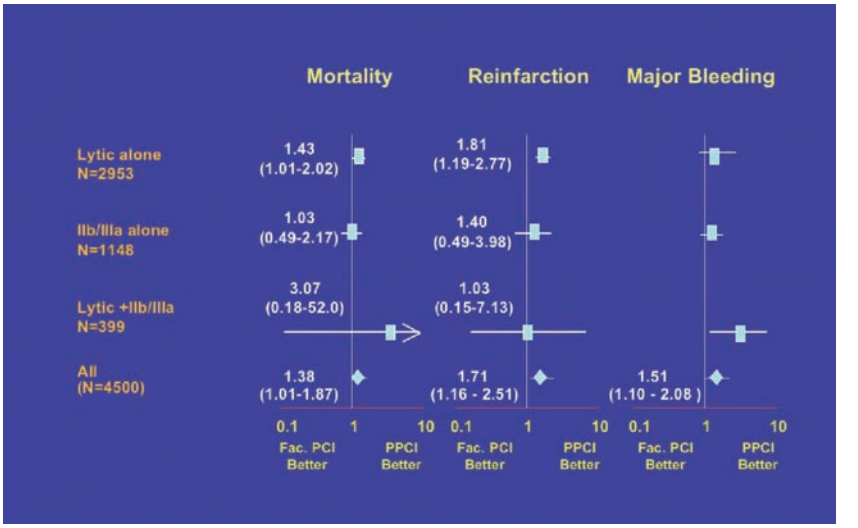


Fig. 3.5 Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction. The results of three pharmacologic reperfusion strategies (lytic alone, GP IIb/IIIa inhibitor alone, or a combination of lytic + GP IIb/IIIa inhibitor) are compared with primary percutaneous coronary intervention (PPCI) for patients with STEMI. Data are shown for mortality, reinfarction, and major bleeding. Adapted from data in Keeley *et al.*, Lancet. 2006;367:579.

Table 3.3 Meta-analysis: rescue PCI vs. conservative therapy

Outcome	Rescue PCI	*N*	Conservative treatment	*N*	RR (95% CI)	*P*
Mortality (%)	7.3	454	10.4	457	0.69 (0.46–1.05)	0.09
HF (%)	12.7	424	17.8	427	0.73 (0.54–1.00)	0.05
Reinfarction (%)	6.1	346	10.7	354	0.58 (0.35–0.97)	0.04
Stroke (%)	3.4	297	0.7	295	4.98 (1.10–22.48)	0.04
Minor bleeding (%)	16.6	313	3.6	307	4.58 (2.46–8.55)	<0.001

In three trials enrolling 700 patients that reported the composite end point of all-cause mortality, reinfarction, and HF, rescue PCI was associated with a significant RR reduction of 28% (RR 0.72; 95% CI, 0.59–0.88; $P = 0.001$). Note: *N* refers to the total number of patients from available trials for whom data were available for the endpoint shown. Percentages refer to the proportion of patients (*N*) experiencing the endpoint.
Adapted from data in Wijeysundera HC, *et al.* J Am Coll Cardiol. 2007;49:422–30.

for revascularization *(Level of Evidence: B)*; (b) severe congestive heart failure and/or pulmonary edema (Killip class III) *(Level of Evidence: B)*; (c) hemodynamically compromising ventricular arrhythmias *(Level of Evidence: C)*

Class IIa

1 A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is reasonable in patients 75 years or older who have received fibrinolytic therapy, and are in cardiogenic shock, provided they are suitable candidates for revascularization *(Level of Evidence: B)*

2 It is reasonable to perform rescue PCI for patients with 1 or more of the following:

a. Hemodynamic or electrical instability *(Level of Evidence: C)*

b. Persistent ischemic symptoms. *(Level of Evidence: C)*

3 A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation less than 50% resolved after 90 min following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and a moderate or large area of myocardium at risk (anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression). *(Level of Evidence: B)*

Class IIb

A strategy of coronary angiography with intent to perform PCI in the absence of any of the above Class I or IIa indications might be reasonable but its benefits and risks are not well established. The benefits of rescue PCI are greater the earlier it is initiated after the onset of ischemic discomfort. *(Level of Evidence: C)*

Class III

A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is not recommended in patients who have received fibrinolytic therapy if further invasive management is contraindicated or the patient or designee does not wish further invasive care. *(Level of Evidence: C)*

PCI after fibrinolysis or for patients not undergoing primary reperfusion

Class I

1 In patients whose anatomy is suitable, PCI should be performed when there is objective evidence of recurrent MI. *(Level of Evidence: C)*

2 In patients whose anatomy is suitable, PCI should be performed for moderate or severe spontaneous or provocable myocardial ischemia during recovery from STEMI. *(Level of Evidence: B)*
3 In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability. (See section on PCI for cardiogenic shock on page 70.) *(Level of Evidence: B)*

Class IIa

1 It is reasonable to perform routine PCI in patients with LV ejection fraction (LVEF) less than or equal to 0.40, CHF, or serious ventricular arrhythmias. *(Level of Evidence: C)*
2 It is reasonable to perform PCI when there is documented clinical heart failure during the acute episode, even though subsequent evaluation shows preserved LV function (LVEF greater than 0.40). *(Level of Evidence: C)*

Class IIb

PCI of a hemodynamically significant stenosis in a patent infarct artery >24 hours after STEMI may be considered as part of a routine invasive strategy. *(Level of Evidence: B)*

Class III

PCI of a totally occluded infarct artery >24 hours after STEMI is not recommended in asymptomatic patients with one- or two-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia. *(Level of Evidence: B)*

Acute surgical reperfusion

Class I

Emergency or urgent CABG in patients with STEMI should be undertaken in the following circumstances:

a. Failed PCI with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery. *(Level of Evidence: B)*
b. Persistent or recurrent ischemia refractory to medical therapy in patients who have coronary anatomy suitable for surgery, have a significant area of myocardium at risk, and are not candidates for PCI or fibrinolytic therapy. *(Level of Evidence: B)*
c. At the time of surgical repair of postinfarction ventricular septal rupture (VSR) or mitral valve insufficiency. *(Level of Evidence: B)*
d. Cardiogenic shock in patients less than 75 years old with ST elevation, LBBB, or posterior MI who develop shock within 36 hours of STEMI, have severe multivessel or left main disease, and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*
e. Life-threatening ventricular arrhythmias in the presence of greater than or equal to 50% left main stenosis and/or triple-vessel disease. *(Level of Evidence: B)*

Class IIa

1 Emergency CABG can be useful as the primary reperfusion strategy in patients who have suitable anatomy, who are not candidates for fibrinolysis or PCI, and who are in the early hours (6 to 12 hours) of an evolving STEMI, especially if severe multivessel or left main disease is present. *(Level of Evidence: B)*
2 Emergency CABG can be effective in selected patients 75 years or older with ST elevation, LBBB, or posterior MI who develop shock within 36 hours of STEMI, have severe triple-vessel or left main disease, and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

Class III

1 Emergency CABG should not be performed in patients with persistent angina and a small area of risk if they are hemodynamically stable. *(Level of Evidence: C)*
2 Emergency CABG should not be performed in patients with successful epicardial reperfusion but unsuccessful microvascular reperfusion. *(Level of Evidence: C)*

Assessment of reperfusion

Class IIa

It is reasonable to monitor the pattern of ST elevation, cardiac rhythm, and clinical symptoms over

the 60 to 180 minutes after initiation of fibrinolytic therapy. Noninvasive findings suggestive of reperfusion include relief of symptoms, maintenance or restoration of hemodynamic and or electrical stability, and a reduction of at least 50% of the initial ST-segment elevation injury pattern on a follow-up ECG 60 to 90 minutes after initiation of therapy. *(Level of Evidence: B)*

Ancillary therapy [2]

Anticoagulants as ancillary therapy to reperfusion therapy See Table 3.4.

1 Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours *(Level of Evidence: C)* and preferably for the duration of the index hospitalization, up to 8 days (regimens other than UFH are recommended if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). *(Level of Evidence: A)*

Anticoagulant regimens with established efficacy include:

a. UFH (initial intravenous bolus 60 U/kg [maximum 4000 U]) followed by an intravenous infusion of 12 U/kg/h (maximum 1000 U/h) initially, adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds) *(Level of Evidence: C)*. (Note: the available data do not

Table 3.4 Summary of observations from trials of anticoagulants for STEMI

Anticoagulant	Efficacy (through 30 days)	Safety	Use during PCI
Reviparin	Fibrinolysis: probably superior to placebo* No reperfusion: probably superior to placebo*	Increased risk of serious bleeds†	No data on reviparin alone during PCI. Additional anticoagulant with anti-IIa activity, such as UFH or bivalirudin, recommended.
Fondaparinux	Fibrinolysis: appears superior to control therapy (placebo/UFH). Relative benefit versus placebo and UFH separately cannot be reliably determined from available data.* Primary PCI: when used alone, no advantage over UFH and trend toward worse outcome (see "Use During PCI") No reperfusion: appears superior to control therapy (placebo/UFH). Relative benefit versus placebo and UFH separately cannot be reliably determined from available data.*	Trend toward decreased risk of serious bleeds†	Increased risk of catheter thrombosis when fondaparinux used alone. Additional anticoagulant with anti-IIa activity, such as UFH or bivalirudin, recommended.
Enoxaparin	Fibrinolysis: appears superior to UFH	Increased risk of serious bleeds†	Enoxaparin can be used to support PCI after fibrinolysis. No additional anticoagulant needed.

* See text of focused update (Antman *et al.*, Circulation. 2008;117:296–329) for further discussion and subgroup analysis. †Definitions of significant bleeds varied among trials. Consult original references for details.

PCI indicates percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and UFH, unfractionated heparin.

suggest a benefit of prolonging the duration of the infusion of UFH beyond 48 hours in the absence of ongoing indications for anticoagulation; more prolonged infusions of UFH increase the risk of development of heparin-induced thrombocytopenia.)

b. Enoxaparin (provided the serum creatinine is less than 2.5 mg/dL in men and 2.0 mg/dL in women): for patients less than 75 years of age, an initial 30 mg intravenous bolus is given, followed 15 minutes later by subcutaneous injections of 1.0 mg/kg every 12 hours; for patients at least 75 years of age, the initial intravenous bolus is eliminated and the subcutaneous dose is reduced to 0.75 mg/kg every 12 hours. Regardless of age, if the creatinine clearance (using the Cockroft–Gault formula) during the course of treatment is estimated to be less than 30 mL/min, the subcutaneous regimen is 1.0 mg/kg every 24 hours. Maintenance dosing with enoxaparin should be continued for the duration of the index hospitalization, up to 8 days. *(Level of Evidence: A)*

c. Fondaparinux (provided the serum creatinine is less than 3.0 mg/dL): Initial dose 2.5 mg intravenously; subsequently subcutaneous injections of 2.5 mg once daily. Maintenance dosing with fondaparinux should be continued for the duration of the index hospitalization, up to 8 days. *(Level of Evidence: B)*

2 For patients undergoing PCI after having received an anticoagulant regimen, the following dosing recommendations should be followed:

a. For prior treatment with UFH, administer additional boluses of UFH as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. *(Level of Evidence: C)* Bivalirudin may also be used in patients treated previously with UFH. *(Level of Evidence: C)*

b. For prior treatment with enoxaparin: if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered at least 8 to 12 hours earlier, an intravenous dose of 0.3 mg/kg of enoxaparin should be given. *(Level of Evidence: B)*

c. For prior treatment with fondaparinux, administer additional intravenous treatment with an anticoagulant possessing anti-IIa activity taking into account whether GP IIb/IIIa receptor antagonists have been administered. *(Level of Evidence: C)*

Class III

Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered. *(Level of Evidence: C)*

Antiplatelets

Aspirin

Class I

1 A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy. *(Level of Evidence: A)*

Thienopyridines [2]

Class I

1 Clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. *(Level of Evidence: A)* Treatment with clopidogrel should continue for at least 14 days *(Level of Evidence: B).*

2 In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of excess bleeding. *(Level of Evidence: B)*

Class IIa

1 Clopidogrel is probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. *(Level of Evidence: C)*

2 In patients less than age 75 years who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral clopidogrel loading dose of 300 mg. *(Level of Evidence: C)* (No data are available to guide decision making regarding an oral loading dose in patients greater than or equal to 75 years of age.)

3 Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo

reperfusion with fibrinolytic therapy or do not receive reperfusion therapy *(Level of Evidence: C)*

Glycoprotein IIb/IIIa inhibitors

Class IIa

It is reasonable to start treatment with abciximab as early as possible before primary PCI (with or without stenting) in patients with STEMI. *(Level of Evidence: B)*

Class IIb

Treatment with tirofiban or eptifibatide may be considered before primary PCI (with or without stenting) in patients with STEMI. *(Level of Evidence: C)*

Other pharmacological measures

Inhibition of renin–angiotensin–aldosterone system

Class I

1 An angiotensin converting enzyme (ACE) inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF less than 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. *(Level of Evidence: A)*

2 An angiotensin receptor blocker (ARB) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. *(Level of Evidence: C)*

Class IIa

An ACE inhibitor administered orally within the first 24 hours of STEMI can be useful in patients without anterior infarction, pulmonary congestion, or LVEF less than 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. The expected treatment benefit in such patients is less (five lives saved per 1000 patients treated) than for patients with LV dysfunction. *(Level of Evidence: B)*

Class III

An intravenous ACE inhibitor should not be given to patients within the first 24 hours of STEMI because of the risk of hypotension. (A possible exception may be patients with refractory hypertension.) *(Level of Evidence: B)*

Metabolic modulation of the glucose–insulin axis

Strict glucose control during STEMI

Class I

An insulin infusion to normalize blood glucose is recommended for patients with STEMI and complicated courses. *(Level of Evidence: B)*

Class IIa

1 During the acute phase (first 24 to 48 hours) of the management of STEMI in patients with hyperglycemia, it is reasonable to administer an insulin infusion to normalize blood glucose, even in patients with an uncomplicated course. *(Level of Evidence: B)*

2 After the acute phase of STEMI, it is reasonable to individualize treatment of diabetics, selecting from a combination of insulin, insulin analogs, and oral hypoglycemic agents that achieve the best glycemic control and are well tolerated. *(Level of Evidence: C)*

Magnesium

Class IIa

1 It is reasonable that documented magnesium deficits be corrected, especially in patients receiving diuretics before the onset of STEMI. *(Level of Evidence: C)*

2 It is reasonable that episodes of torsade de pointes-type ventricular tachycardia (VT) associated with a prolonged QT interval be treated with 1 to 2 g of magnesium administered as an intravenous bolus over 5 minutes. *(Level of Evidence: C)*

Class III

In the absence of documented electrolyte deficits or torsade de pointes-type VT, routine intravenous magnesium should not be administered to STEMI patients at any level of risk. *(Level of Evidence: A)*

Calcium channel blockers

Class IIa

It is reasonable to give verapamil or diltiazem to patients in whom beta-blockers are ineffective or contraindicated (e.g., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ven-

tricular response with atrial fibrillation or flutter after STEMI in the absence of CHF, LV dysfunction, or atrioventricular (AV) block. *(Level of Evidence: C)*

Class III

1 Diltiazem and verapamil are contraindicated in patients with STEMI and associated systolic LV dysfunction and CHF. *(Level of Evidence: A)*

2 Nifedipine (immediate-release form) is contraindicated in treatment of STEMI because of the reflex sympathetic activation, tachycardia, and hypotension associated with its use. *(Level of Evidence: B)*

Hospital management

See Table 3.5 for sample admitting orders.

Table 3.5 Sample admitting orders for the STEMI patient

1. **Condition: serious**
2. **IV: NS on D_5W** to keep vein open. Start a second IV if IV medication is being given. This may be a saline lock
3. **Vital signs**: every 1.5 hours until stable, then every 4 hours and as needed. Notify physician if HR is less than 60 bpm or greater than 100 bpm, BP is less than 100 mm Hg systolic or greater than 150 mm Hg systolic, respiratory rate is less than 8 or greater than 22
4. **Monitor**: Continuous ECG monitoring for arrhythmia and ST segment deviation
5. **Diet**: NPO except for sips of water until stable. Then start 2 gram sodium/day, low saturated fat (less than 7% of total calories/day), low cholesterol (less than 200 mg/day) diet, such as Total Lifestyle Change (TLC) diet
6. **Activity**: Bedside commode and light activity when stable
7. **Oxygen**: Continuous oximetry monitoring. Nasal cannula at 2 liters/min when stable for 6 hours, re-assess for oxygen need, (i.e., O_2 saturation less than 90%) and consider discontinuing oxygen.
8. **Medications**:
   a. **Nitroglycerin (NTG)**
      1. Use sublingual NTG 0.4 mg every 5 minutes as needed for chest discomfort.
      2. Intravenous NTG for CHF, hypertension, or persistent ischemia.
   b. **ASA**
      1. If ASA not given in the emergency department (ED), chew non-enteric-coated ASA† 162 to 325 mg
      2. If ASA has been given, start daily maintenance of 75 to 162 mg daily. May use enteric-coated formulation for GI protection.
   c. **Beta-blocker**
      1. If not given in the ED, assess for contraindications, i.e., bradycardia and hypotension. Continue daily assessment to ascertain eligibility for beta blocker
      2. If given in the ED, continue daily dose and optimize as dictated by heart rate and blood pressure
   d. **ACE inhibitor**
      1. Start ACE inhibitor orally in patients with pulmonary congestion or LVEF less than 40% if the following are absent: hypotension (SBP less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to this class of medications
   e. **Angiotensin receptor blocker (ARB)**
      1. Start ARB orally in patients who are intolerant of ACE inhibitors and with either clinical or radiological signs of heart failure or LVEF less than 40%.
   f. **Pain meds**
      2. IV morphine sulfate 2 to 4 mg with increments of 2 to 8 mg IV at 5 to 15 minute intervals as needed to control pain.
   g. **Anxiolytics** (based on a nursing assessment)
   h. **Daily stool softener**
9. **Laboratory tests**: Serum biomarkers for cardiac damage*, CBC with platelet count, INR, aPTT, electrolytes, magnesium, BUN, creatinine, glucose, serum lipids (See Table 9 in the STEMI guideline).

*Do not wait for results before implementing reperfusion strategy.

†Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations.

Modified from: Entman *et al.* Circulation. 2004;110:e82–e292..

A. Location

1. Coronary care unit

Class I

1 STEMI patients should be admitted to a quiet and comfortable environment that provides for continuous monitoring of the ECG and pulse oximetry and has ready access to facilities for hemodynamic monitoring and defibrillation. *(Level of Evidence: C)*

2 The patient's medication regimen should be reviewed to confirm the administration of aspirin and beta-blockers in an adequate dose to control heart rate and to assess the need for intravenous nitroglycerin for control of angina, hypertension, or heart failure. *(Level of Evidence: A)*

3 The ongoing need for supplemental oxygen should be assessed by monitoring arterial oxygen saturation. When stable for 6 hours, the patient should be reassessed for oxygen need (i.e., O_2 saturation of less than 90%), and discontinuation of supplemental oxygen should be considered. *(Level of Evidence: C)*

4 Nursing care should be provided by individuals certified in critical care, with staffing based on the specific needs of patients and provider competencies, as well as organizational priorities. *(Level of Evidence: C)*

5 Care of STEMI patients in the critical care unit (CCU) should be structured around protocols derived from practice guidelines. *(Level of Evidence: C)*

6 Electrocardiographic monitoring leads should be based on the location and rhythm to optimize detection of ST deviation, axis shift, conduction defects, and dysrhythmias. *(Level of Evidence: B)*

Class III

It is not an effective use of the CCU environment to admit terminally ill, "do not resuscitate" patients with STEMI, because clinical and comfort needs can be provided outside of a critical care environment. *(Level of Evidence: C)*

2. Stepdown unit

Class I

1 It is a useful triage strategy to admit low-risk STEMI patients who have undergone successful PCI directly to the stepdown unit for post-PCI care rather than to the CCU. *(Level of Evidence: C)*

2 STEMI patients originally admitted to the CCU who demonstrate 12 to 24 hours of clinical stability (absence of recurrent ischemia, heart failure, or hemodynamically compromising dysrhythmias) should be transferred to the stepdown unit. *(Level of Evidence: C)*

Class IIa

1 It is reasonable for patients recovering from STEMI who have clinically symptomatic heart failure to be managed on the stepdown unit, provided that facilities for continuous monitoring of pulse oximetry and appropriately skilled nurses are available. *(Level of Evidence: C)*

2 It is reasonable for patients recovering from STEMI who have arrhythmias that are hemodynamically well-tolerated (e.g., atrial fibrillation with a controlled ventricular response; paroxysms of nonsustained VT lasting less than 30 seconds) to be managed on the stepdown unit, provided that facilities for continuous monitoring of the ECG, defibrillators, and appropriately skilled nurses are available. *(Level of Evidence: C)*

Class IIb

Patients recovering from STEMI who have clinically significant pulmonary disease requiring high-flow supplemental oxygen or noninvasive mask ventilation/bilevel positive airway pressure (BIPAP)/continuous positive airway pressure (CPAP) may be considered for care on a stepdown unit provided that facilities for continuous monitoring of pulse oximetry and appropriately skilled nurses with a sufficient nurse : patient ratio are available. *(Level of Evidence: C)*

B. Early, general measures

1. Level of activity

Class IIa

After 12 to 24 hours, it is reasonable to allow patients with hemodynamic instability or continued ischemia to have bedside commode privileges. *(Level of Evidence: C)*

Class III

Patients with STEMI who are free of recurrent ischemic discomfort, symptoms of heart failure, or serious disturbances of heart rhythm should not be on bed rest for more than 12 to 24 hours. *(Level of Evidence: C)*

2. Diet

Class I

1 Patients with STEMI should be prescribed the NCEP Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet, which focuses on reduced intake of fats and cholesterol, less than 7% of total calories as saturated fats, less than 200 mg of cholesterol per day, increased consumption of omega-3 fatty acids, and appropriate caloric intake for energy needs. *(Level of Evidence: C)*

2 Diabetic patients with STEMI should have an appropriate food group balance and caloric intake. *(Level of Evidence: B)*

3 Sodium intake should be restricted in STEMI patients with hypertension or heart failure. *(Level of Evidence: B)*

3. Patient education in the hospital setting

Class I

1 Patient counseling to maximize adherence to evidence-based post-STEMI treatments (e.g., compliance with taking medication, exercise prescription, and smoking cessation) should begin during the early phase of hospitalization, occur intensively at discharge, and continue at follow-up visits with providers and through cardiac rehabilitation programs and community support groups, as appropriate. *(Level of Evidence: C)*

2 Critical pathways and protocols and other quality improvement tools (e.g., the ACC "Guidelines Applied in Practice" and the AHA's "Get with the Guidelines") should be used to improve the application of evidence-based treatments by patients with STEMI, caregivers, and institutions. *(Level of Evidence: C)*

4. Analgesia/anxiolytics

Class IIa

1 It is reasonable to use anxiolytic medications in STEMI patients to alleviate short-term anxiety or altered behavior related to hospitalization for STEMI. *(Level of Evidence: C)*

2 It is reasonable to routinely assess the patient's anxiety level and manage it with behavioral interventions and referral for counseling. *(Level of Evidence: C)*

C. Medication assessment

1. Beta-blockers

Class I

1 Patients receiving beta-blockers within the first 24 hours of STEMI without adverse effects should continue to receive them during the early convalescent phase of STEMI. *(Level of Evidence: A)*

2 Patients without contraindications to beta-blockers who did not receive them within the first 24 hours after STEMI should have them started in the early convalescent phase. *(Level of Evidence: A)*

3 Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for beta-blocker therapy. *(Level of Evidence: C)*

2. Nitroglycerin

Class I

1 Intravenous nitroglycerin is indicated in the first 48 hours after STEMI for treatment of persistent ischemia, CHF, or hypertension. The decision to administer intravenous nitroglycerin and the dose used should not preclude therapy with other proven mortality-reducing interventions, such as beta-blockers or ACE inhibitors. *(Level of Evidence: B)*

2 Intravenous, oral, or topical nitrates are useful beyond the first 48 hours after STEMI for treatment of recurrent angina or persistent CHF if their use does not preclude therapy with beta-blockers or ACE inhibitors. *(Level of Evidence: B)*

Class IIb

The continued use of nitrate therapy beyond the first 24 to 48 hours in the absence of continued or recurrent angina or CHF may be helpful, although the benefit is likely to be small and is not well established in contemporary practice. *(Level of Evidence: B)*

Class III

Nitrates should not be administered to patients with systolic pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 bpm), tachycardia (more than 100 bpm) or RV infarction. *(Level of Evidence: C)*

3. Inhibition of the renin–angiotensin–aldosterone system

Class I

1 An ACE inhibitor should be administered orally during convalescence from STEMI in patients who tolerate this class of medication, and it should be continued over the long term. *(Level of Evidence: A)*

2 An ARB should be administered to STEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of heart failure or LVEF less than 0.40. Valsartan and candesartan have demonstrated efficacy for this recommendation. *(Level of Evidence: B)*

3 Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 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 heart failure or diabetes. *(Level of Evidence: A)*

Class IIa

In STEMI patients who tolerate ACE inhibitors, an ARB can be useful as an alternative to ACE inhibitors provided there are either clinical or radiological signs of heart failure or LVEF is less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. *(Level of Evidence: B)*

4. Antiplatelets

Class I

1 Aspirin 162 to 325 mg should be given on day 1 of STEMI and in the absence of contraindications should be continued indefinitely on a daily basis thereafter at a dose of 75 to 162 mg. *(Level of Evidence: A)*

2 A thienopyridine (preferably clopidogrel) should be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. *(Level of Evidence: C)*

3 For patients taking clopidogrel for whom CABG is planned, if possible, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of bleeding. *(Level of Evidence: B)*

4 For patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation and for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel) and up to 12 months in patients who are not at high risk for bleeding. *(Level of Evidence: B)*

5. Anticoagulants

Class I

Intravenous UFH (bolus of 60 U/kg, maximum 4000 U IV; initial infusion 12 U/kg per hour, maximum of 1000 U/h) or LMWH should be used in patients after STEMI who are at high risk for systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, known LV thrombus, or cardiogenic shock). *(Level of Evidence: C)*

Class IIa

Patients with STEMI who do not undergo reperfusion therapy should be treated with anticoagulant therapy (non-UFH regimen) for the duration of the index hospitalization, up to 8 days. *(Level of Evidence: B)* Convenient strategies that can be used include those with LMWH *(Level of Evidence: C)* or fondaparinux *(Level of Evidence: B)* using the same dosing regimens as for patients who receive fibrinolytic therapy.

6. Oxygen

Class I

Supplemental oxygen therapy should be continued beyond the first 6 hours in STEMI patients with arterial oxygen desaturation (SaO_2 less than 90%) or overt pulmonary congestion. *(Level of Evidence: C)*

D. Estimation of infarct size

1. Electrocardiographic techniques

Class I

All patients with STEMI should have follow-up ECGs at 24 hours and at hospital discharge to assess the success of reperfusion and/or the extent of infarction, defined in part by the presence or absence of new Q waves. *(Level of Evidence: B)*

E. Hemodynamic disturbances

1. Hemodynamic assessment

Class I

1 Pulmonary artery catheter monitoring should be performed for the following:

a. Progressive hypotension, when unresponsive to fluid administration or when fluid administration may be contraindicated. *(Level of Evidence: C)*

b. Suspected mechanical complications of STEMI, (i.e., VSR, papillary muscle rupture, or free wall rupture with pericardial tamponade) if an echocardiogram has not been performed. *(Level of Evidence: C)*

2 Intra-arterial pressure monitoring should be performed for the following:

a. Patients with severe hypotension (systolic arterial pressure less than 80 mm Hg). *(Level of Evidence: C)*

b. Patients receiving vasopressor/inotropic agents. *(Level of Evidence: C)*

c. Cardiogenic shock. *(Level of Evidence: C)*

Class IIa

1 Pulmonary artery catheter monitoring can be useful for the following:

a. Hypotension in a patient without pulmonary congestion who has not responded to an initial trial of fluid administration. *(Level of Evidence: C)*

b. Cardiogenic shock. *(Level of Evidence: C)*

c. Severe or progressive CHF or pulmonary edema that does not respond rapidly to therapy. *(Level of Evidence: C)*

d. Persistent signs of hypoperfusion without hypotension or pulmonary congestion. *(Level of Evidence: C)*

e. Patients receiving vasopressor/inotropic agents. *(Level of Evidence: C)*

2 Intra-arterial pressure monitoring can be useful for patients receiving intravenous sodium nitroprusside or other potent vasodilators. *(Level of Evidence: C)*

Class IIb

Intra-arterial pressure monitoring might be considered in patients receiving intravenous inotropic agents. *(Level of Evidence: C)*

Class III

1 Pulmonary artery catheter monitoring is not recommended in patients with STEMI without evidence of hemodynamic instability or respiratory compromise. *(Level of Evidence: C)*

2 Intra-arterial pressure monitoring is not recommended for patients with STEMI who have no pulmonary congestion and have adequate tissue perfusion without use of circulatory support measures. *(Level of Evidence: C)*

2. Hypotension

Class I

1 Rapid volume loading with an IV infusion should be administered to patients without clinical evidence for volume overload. *(Level of Evidence: C)*

2 Rhythm disturbances or conduction abnormalities causing hypotension should be corrected. *(Level of Evidence: C)*

3 Intra-aortic balloon counterpulsation should be performed in patients who do not respond to other interventions, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: B)*

4 Vasopressor support should be given for hypotension that does not resolve after volume loading. *(Level of Evidence: C)*

5 Echocardiography should be used to evaluate mechanical complications unless these are assessed by invasive measures. *(Level of Evidence: C)*

3. Low-output state

Class I

1 LV function and potential presence of a mechanical complication should be assessed by echocardiography if these have not been evaluated by invasive measures. *(Level of Evidence: C)*

2 Recommended treatments for low-output states include:

a. Inotropic support. *(Level of Evidence: B)*

b. Intra-aortic counterpulsation. *(Level of Evidence: B)*

c. Mechanical reperfusion with PCI or CABG. *(Level of Evidence: B)*

d. Surgical correction of mechanical complications. *(Level of Evidence: B)*

Class III

Beta-blockers or calcium channel antagonists should not be administered to patients in a low-output state due to pump failure. *(Level of Evidence: B)*

4. Pulmonary congestion

Class I

1 Oxygen supplementation to arterial saturation greater than 90% is recommended for patients with pulmonary congestion. *(Level of Evidence: C)*

2 Morphine sulfate should be given to patients with pulmonary congestion. *(Level of Evidence: C)*

3 ACE inhibitors, beginning with titration of a short-acting ACE inhibitor with a low initial dose (e.g., 1 to 6.25 mg of captopril) should be given to patients with pulmonary edema unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. *(Level of Evidence: A)*

4 Nitrates should be administered to patients with pulmonary congestion unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. *(Level of Evidence: C)*

5 A diuretic (low- to intermediate-dose furosemide, or torsemide or bumetanide) should be administered to patients with pulmonary congestion if there is associated volume overload. Caution is advised for patients who have not received volume expansion. *(Level of Evidence: C)*

6 Beta-blockade should be initiated before discharge for secondary prevention. For those who remain in heart failure throughout the hospitalization, low doses should be initiated, with gradual titration on an outpatient basis. *(Level of Evidence: B)*

7 Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 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 heart failure or diabetes. *(Level of Evidence: A)*

8 Echocardiography should be performed urgently to estimate LV and RV function and to exclude a mechanical complication. *(Level of Evidence: C)*

Class IIb

It may be reasonable to insert an intra-aortic balloon pump (IABP) for the management of patients with refractory pulmonary congestion. *(Level of Evidence: C)*

Class III

Beta-blockers or calcium channel blockers should not be administered acutely to STEMI patients with frank cardiac failure evidenced by pulmonary congestion or signs of a low-output state. *(Level of Evidence: B)*

5. Cardiogenic shock

Class I

1 Intra-aortic balloon counterpulsation is recommended for STEMI patients when cardiogenic shock is not quickly reversed with pharmacological therapy. The IABP is a stabilizing measure for angiography and prompt revascularization. *(Level of Evidence: B)*

2 Intra-arterial monitoring is recommended for the management of STEMI patients with cardiogenic shock. *(Level of Evidence: C)*

3 Early revascularization, either PCI or CABG, is recommended for patients less than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*

4 Fibrinolytic therapy should be administered to STEMI patients with cardiogenic shock who are unsuitable for further invasive care and do not have contraindications to fibrinolysis. *(Level of Evidence: B)*

5 Echocardiography should be used to evaluate mechanical complications unless these are assessed by invasive measures. *(Level of Evidence: C)*

Class IIa

1 Pulmonary artery catheter monitoring can be useful for the management of STEMI patients with cardiogenic shock. *(Level of Evidence: C)*

2 Early revascularization, either PCI or CABG, is reasonable for selected patients 75 years or older with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

6. Right ventricular infarction

Class I

1 Patients with inferior STEMI and hemodynamic compromise should be assessed with a right precordial V4R lead to detect ST-segment elevation and an echocardiogram to screen for RV infarction. (See the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography.) *(Level of Evidence: B)*

2 The following principles apply to therapy of patients with STEMI and RV infarction and ischemic dysfunction:

a. Early reperfusion should be achieved if possible. *(Level of Evidence: C)*

b. AV synchrony should be achieved, and bradycardia should be corrected. *(Level of Evidence: C)*

c. RV preload should be optimized, which usually requires initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low. *(Level of Evidence: C)*

d. RV afterload should be optimized, which usually requires therapy for concomitant LV dysfunction. *(Level of Evidence: C)*

e. Inotropic support should be used for hemodynamic instability not responsive to volume challenge. *(Level of Evidence: C)*

Class IIa

After infarction that leads to clinically significant RV dysfunction, it is reasonable to delay CABG surgery for 4 weeks to allow recovery of contractile performance. *(Level of Evidence: C)*

7. Mechanical causes of heart failure/ low-output syndrome

a. Diagnosis

Mechanical defects, when they occur, usually present within the first week after STEMI. On physical examination, the presence of a new cardiac murmur indicates the possibility of either a VSR or MR. Left ventricular free-wall rupture is typically heralded by chest pain and ECG ST-T-wave changes, with rapid progression to hemodynamic collapse and electromechanical dissociation.

b. Mitral valve regurgitation

Class I

1 Patients with acute papillary muscle rupture should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: B)*

2 CABG surgery should be undertaken at the same time as mitral valve surgery. *(Level of Evidence: B)*

c. Ventricular septal rupture after STEMI

Class I

1 Patients with STEMI complicated by the development of a VSR should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: B)*

2 CABG should be undertaken at the same time as repair of the VSR. *(Level of Evidence: B)*

d. Left ventricular free-wall rupture

Class I

1 Patients with free-wall rupture should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: B)*

2 CABG should be undertaken at the same time as repair of free-wall rupture. *(Level of Evidence: C)*

e. Left ventricular aneurysm

Class IIa

It is reasonable that patients with STEMI who develop a ventricular aneurysm associated with intractable ventricular tachyarrhythmias and/or pump failure unresponsive to medical and catheter-based therapy be considered for LV aneurysmectomy and CABG surgery. *(Level of Evidence: B)*

f. Mechanical support of the failing heart

Intra-aortic balloon counterpulsation

Class I

1 Intra-aortic balloon counterpulsation should be used in STEMI patients with hypotension (systolic blood pressure less than 90 mm Hg or 30 mm Hg below baseline mean arterial pressure) who do not respond to other interventions, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. See Section 7.6.2 of the full-text guidelines. *(Level of Evidence: B)*

2 Intra-aortic balloon counterpulsation is recommended for STEMI patients with low-output state. See Section 7.6.3 of the full-text guidelines. *(Level of Evidence: B)*

3 Intra-aortic balloon counterpulsation is recommended for STEMI patients when cardiogenic shock is not quickly reversed with pharmacological therapy. IABP is a stabilizing measure for angiography and prompt revascularization. See Section 7.6.5 of the full-text guidelines. *(Level of Evidence: B)*

4 Intra-aortic balloon counterpulsation should be used in addition to medical therapy for STEMI patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor LV function, or a large area of myocardium at risk. Such patients should be referred urgently for cardiac catheterization and should undergo revascularization as needed. See Section 7.8.2 of the full-text guidelines. *(Level of Evidence: C)*

Class IIa

It is reasonable to manage STEMI patients with refractory polymorphic VT with intra-aortic balloon counterpulsation to reduce myocardial ischemia. See Section 7.7.1.2 of the full-text guidelines. *(Level of Evidence: B)*

Class IIb

It may be reasonable to use intra-aortic balloon counterpulsation in the management of STEMI patients with refractory pulmonary congestion. See Section 7.6.4 of the full-text guidelines. *(Level of Evidence: C)*

F. Arrhythmias after STEMI

1. Ventricular arrhythmias

a. Ventricular fibrillation

Class I

Ventricular fibrillation (VF) or pulseless VT should be treated with an unsynchronized electric shock with an initial monophasic shock energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and then, if necessary, a third shock of 360 J. *(Level of Evidence: B)*

Class IIa

1 It is reasonable that VF or pulseless VT that is refractory to electrical shock be treated with amiodarone (300 mg or 5 mg/kg, IV bolus) followed by a repeat unsynchronized electric shock. *(Level of Evidence: B)*

2 It is reasonable to correct electrolyte and acid-base disturbances (potassium greater than 4.0 mEq/L and magnesium greater than 2.0 mg/dL) to prevent recurrent episodes of VF once an initial episode of VF has been treated. *(Level of Evidence: C)*

Class IIb

It may be reasonable to treat VT or shock-refractory VF with boluses of intravenous procainamide. However, this has limited value owing to the length of time required for administration. *(Level of Evidence: C)*

Class III

Prophylactic administration of antiarrhythmic therapy is not recommended when using fibrinolytic agents. *(Level of Evidence: B)*

b. Ventricular tachycardia

Class I

1 Sustained (more than 30 seconds or causing hemodynamic collapse) polymorphic VT should be treated with an unsynchronized electric shock with an initial monophasic shock energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J. *(Level of Evidence: B)*

2 Episodes of sustained monomorphic VT associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with a synchronized electric shock of 100 J initial monophasic shock energy. Increasing energies may be used if not initially successful. Brief anesthesia is desirable if hemodynamically tolerable. *(Level of Evidence: B)*

3 Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with:

a. Amiodarone: 150 mg infused over 10 minutes (alternative dose 5 mg/kg); repeat 150 mg every 10 to 15 minutes as needed. Alternative infusion: 360 mg over 6 hours (1 mg/min), then 540 mg over the next 18 hours (0.5 mg/min). The total cumulative dose, including additional doses given during cardiac arrest, must not exceed 2.2 g over 24 hours. *(Level of Evidence: B)*
b. Synchronized electrical cardioversion starting at monophasic energies of 50 J (brief anesthesia is necessary). *(Level of Evidence: B)*

Class IIa

It is reasonable to manage refractory polymorphic VT by:

a. Aggressive attempts to reduce myocardial ischemia and adrenergic stimulation, including therapies such as beta-adrenoceptor blockade, IABP use, and consideration of emergency PCI/CABG surgery. *(Level of Evidence: B)*
b. Aggressive normalization of serum potassium to greater than 4.0 mEq/L and of magnesium to greater than 2.0 mg/dL. *(Level of Evidence: C)*
c. If the patient has bradycardia to a rate less than 60 beats per minute or long QTc, temporary pacing at a higher rate may be instituted. *(Level of Evidence: C)*

Class IIb

It may be useful to treat sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) with a procainamide bolus and infusion. *(Level of Evidence: C)*

Class III

1 The routine use of prophylactic antiarrhythmic drugs (i.e., lidocaine) is not indicated for suppression of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, or nonsustained VT. *(Level of Evidence: B)*
2 The routine use of prophylactic antiarrhythmic therapy is not indicated when fibrinolytic agents are administered. *(Level of Evidence: B)*

c. Ventricular premature beats

Class III

Treatment of isolated ventricular premature beats, couplets, and nonsustained VT is not recommended unless they lead to hemodynamic compromise. *(Level of Evidence: A)*

d. Accelerated idioventricular rhythms and accelerated junctional rhythms

Class III

1 Antiarrhythmic therapy is not indicated for accelerated idioventricular rhythm. *(Level of Evidence: C)*
2 Antiarrhythmic therapy is not indicated for accelerated junctional rhythm. *(Level of Evidence: C)*

e. Implantable cardioverter defibrillator implantation in patients after STEMI

See Figure 3.6.

The following information from the ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (VA & SCD) [16] is relevant to patients with STEMI. Therefore, selected recommendations from the 2004 STEMI Guidelines noted below have been updated for consistence with the VA & SCD Guidelines.

Recommendations for prophylactic ICD implantation based on ejection fractions (EFs) have been inconsistent because clinical investigators have chosen different EFs for enrollment in trials of therapy, average values of the EF in such trials have been substantially lower than the cutoff value for enrollment,

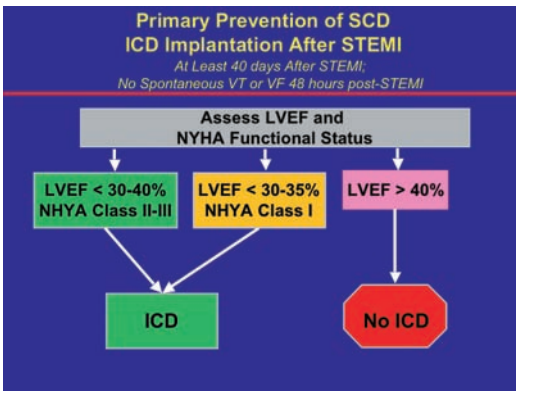


Fig. 3.6 Algorithm for selection of patients for implantation of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death after STEMI. Adapted from recommendations in ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and Prevention of Sudden Cardiac Death, Circulation. 2006;114:e385.

and subgroup analyses of clinical trial populations based on EF have not been consistent in their implications. Substantial differences between guidelines have resulted. However, no trial has randomized patients with an intermediate range of EFs. For instance, there is no trial that has specifically studied patients with an LVEF between 31% and 35%, yet recommendations have been set for such patients on the basis of data derived from trials that studied groups with EFs less than or equal to 30%, others that enrolled patients with an EF less than or equal to 35%, and one trial that enrolled patients with an EF less than or equal to 40%. Recognizing these inconsistencies, recommendations were constructed to apply to patients with an EF less than or equal to a range of values. The highest appropriate class of recommendation was then based on all trials that recruited patients with EFs within this range. In this way, potential conflicts between guidelines were reduced and errors due to drawing false conclusions relating to unstudied patient groups were minimized.

Class I

1 An implantable cardioverter-defibrillator (ICD) is indicated for patients with VF or hemodynamically significant sustained VT more than 2 days after STEMI, provided the arrhythmia is not judged to be due to transient or reversible ischemia or reinfarction. *(Level of Evidence: A)*

2 ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)* [From 2006 VA & SCD Guideline]

Class IIa

Implantation of an ICD is reasonable in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)* [From 2006 VA & SCD Guideline]

Class IIb

1 Curative catheter ablation or amiodarone may be considered in lieu of ICD therapy to improve symptoms in patients with LV dysfunction due to prior MI and recurrent hemodynamically stable VT whose LVEF is greater than 40%. *(Level of Evidence: B)* [From 2006 VA & SCD Guideline]

2 Amiodarone may be reasonable therapy for patients with LV dysfunction due to prior MI with an ICD indication, as defined above, in patients who cannot or refuse to have an ICD implanted. *(Level of Evidence: C)* [From 2006 VA & SCD Guideline]

Class III

An ICD is not indicated in STEMI patients who do not experience spontaneous VF or sustained VT more than 48 hours after STEMI and in whom the LVEF is greater than 0.40 at least 1 month after STEMI. *(Level of Evidence: C)*

2. Supraventricular arrhythmias/atrial fibrillation

Class I

1 Sustained atrial fibrillation and atrial flutter in patients with hemodynamic compromise or ongoing ischemia should be treated with one or more of the following:

a. Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. *(Level of Evidence: C)*

b. For episodes of atrial fibrillation that do not respond to electrical cardioversion or recur after a brief period of sinus rhythm, the use of antiarrhythmic therapy aimed at slowing the ventricular response is indicated. One or more of these pharmacological agents may be used:

i. Intravenous amiodarone. *(Level of Evidence: C)*

ii. Intravenous digoxin for rate control principally for patients with severe LV dysfunction and heart failure. *(Level of Evidence: C)*

2 Sustained atrial fibrillation and atrial flutter in patients with ongoing ischemia but without hemodynamic compromise should be treated with one or more of the following:

a. Beta-adrenergic blockade is preferred, unless contraindicated. *(Level of Evidence: C)*

b. Intravenous diltiazem or verapamil. *(Level of Evidence: C)*

c. Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. *(Level of Evidence: C)*

3 For episodes of sustained atrial fibrillation or flutter without hemodynamic compromise or ischemia, rate control is indicated. In addition, patients with sustained atrial fibrillation or flutter should be given anticoagulant therapy. Consideration should be given to cardioversion to sinus rhythm in patients with a history of atrial fibrillation or flutter prior to STEMI. *(Level of Evidence: C)*

4 Reentrant paroxysmal supraventricular tachycardia, because of its rapid rate, should be treated with the following in the sequence shown:

a. Carotid sinus massage. *(Level of Evidence: C)*

b. Intravenous adenosine (6 mg × 1 over 1 to 2 seconds; if no response, 12 mg IV after 1 to 2 minutes may be given; repeat 12 mg dose if needed). *(Level of Evidence: C)*

c. Intravenous beta-adrenergic blockade with metoprolol (2.5 to 5.0 mg every 2 to 5 minutes to a total of 15 mg over 10 to 15 minutes) or atenolol (2.5 to 5.0 mg over 2 minutes to a total of 10 mg in 10 to 15 minutes). *(Level of Evidence: C)*

d. Intravenous diltiazem (20 mg [0.25 mg/kg]) over 2 minutes followed by an infusion of 10 mg/h). *(Level of Evidence: C)*

e. Intravenous digoxin, recognizing that there may be a delay of at least 1 hour before pharmacological effects appear (8 to 15 mcg/kg [0.6 to 1.0 mg in a person weighing 70 kg]). *(Level of Evidence: C)*

Class III

Treatment of atrial premature beats is not indicated. *(Level of Evidence: C)*

3. Bradyarrhythmias

a. Acute treatment of conduction disturbances and bradyarrhythmias

Ventricular asystole

Class I

Prompt resuscitative measures, including chest compressions, atropine, vasopressin, epinephrine, and temporary pacing, should be administered to treat ventricular asystole. *(Level of Evidence: B)*

b. Use of permanent pacemakers

Pacing for bradycardia or conduction blocks associated with STEMI

See Table 3.6.

Class I

1 Permanent ventricular pacing is indicated for persistent second-degree AV block in the His–Purkinje system with bilateral bundle-branch block or third-degree AV block within or below the His–Purkinje system after STEMI. *(Level of Evidence: B)*

2 Permanent ventricular pacing is indicated for transient advanced second- or third-degree infranodal AV block and associated bundle-branch block. If the site of block is uncertain, an electrophysiological study may be necessary. *(Level of Evidence: B)*

3 Permanent ventricular pacing is indicated for persistent and symptomatic second- or third-degree AV block. *(Level of Evidence: C)*

Class IIb

Permanent ventricular pacing may be considered for persistent second- or third-degree AV block at the AV node level. *(Level of Evidence: B)*

Class III

1 Permanent ventricular pacing is not recommended for transient AV block in the absence of intraventricular conduction defects. *(Level of Evidence: B)*

2 Permanent ventricular pacing is not recommended for transient AV block in the presence of isolated left anterior fascicular block. *(Level of Evidence: B)*

3 Permanent ventricular pacing is not recommended for acquired left anterior fascicular block in the absence of AV block. *(Level of Evidence: B)*

4 Permanent ventricular pacing is not recommended for persistent first-degree AV block in the presence of bundle-branch block that is old or of indeterminate age. *(Level of Evidence: B)*

Sinus node dysfunction after STEMI

Class I

Symptomatic sinus bradycardia, sinus pauses greater than 3 seconds, or sinus bradycardia with a heart rate less than 40 bpm and associated hypotension or signs of systemic hemodynamic compromise should be treated with an intravenous bolus of atropine 0.6 to 1.0 mg. If bradycardia is persistent and maximal

Table 3.6 Recommendations for treatment of atrioventricular and intraventricular conduction disturbances during STEMI

Atrioventricular conduction														
Intraventricular conduction			**First degree AV block**				**Mobitz I second degree AV block**				**Mobitz II second degree AV block**			
	Normal		**Anterior MI**		**Non-anterior MI**		**Anterior MI**		**Non-anterior MI**		**Anterior MI**		**Non-anterior MI**	
Normal	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**
	Observe	I	Observe	I	Observe	I	Observe	IIb	Observe	IIa	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	III	TC	IIb	TC	IIb	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	III	TV	III	TV	III	TV	III	TV	IIa	TV	IIa
Old or New fascicular block (LAFB or LPFB)	Observe	I	Observe	IIb	Observe	IIb	Observe	IIb	Observe	IIb	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	I	TC	IIa	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	III	TV	III	TV	III	TV	III	TV	IIa	TV	IIb
Old bundle branch block	Observe	I	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	I	TC	I	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	IIb	TV	IIb	TV	IIb	TV	IIb	TV	IIa	TV	IIa
New bundle branch block	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	I	TC	I	TC	I	TC	I	TC	I	TC	IIb	TC	IIb
	TV	IIb	TV	IIa	TV	IIa	TV	IIa	TV	IIa	TV	I	TV	I

Fascicular block + RBBB	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	I	TC	I	TC	I	TC	I	TC	I	TC	IIb	TC	IIb
	TV	IIb	TV	IIa	TV	IIa	TV	IIa	TV	IIa	TV	I	TV	I
Alternating left and right bundle branch block	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb
	TV	I	TV	I	TV	I	TV	I	TV	I	TV	I	TV	I

Explanation of table:

This table is designed to summarize the atrio-ventricular (column headings) and intra-ventricular (row headings) conduction disturbances that may occur during acute anterior or non-anterior STEMI, the possible treatment options, and the indications for each possible therapeutic option.

Action

There are 4 possible actions, or therapeutic options, listed and classified for each bradyarrhythmia or conduction problem:

1. Observe: continued electrocardiographic monitoring, no further action planned.
2. A, and A*: atropine administered at 0.6 to 1.0 mg intravenously every 5 minutes to up to 0.04 mg/kg. In general, because the increase in sinus rate with atropine is unpredictable, this is to be avoided unless there is *symptomatic bradycardia* that will likely respond to a vagolytic agent – such as sinus bradycardia or Mobitz I, as denoted by the asterisk, above.
3. TC: application of transcutaneous pads and standby transcutaneous pacing with no further progression to transvenous pacing imminently planned.
4. TV: temporary transvenous pacing. It is assumed, but not specified in the table, at the discretion of the clinician, trancutaneous pads will be applied and standby transcutaneous pacing will be in effect as the patient is transferred to the fluoroscopy unit for temporary transvenous pacing.

Class

Each possible therapeutic option is further classified according to ACC/AHA criteria as I, IIa, IIb, and III. There are no randomized trials available that address or compare specific treatment options. Moreover, the data for this table and recommendations are largely derived from observational data of pre-fibrinolytic era databases. Thus, the recommendations above must be taken as recommendations and tempered by the clinical circumstances.

Level of evidence

This table was developed from: (1) published observational case reports and case series; (2) published summaries, not meta-analyses, of these data; and (3) expert opinion, largely from the pre-reperfusion era. There are no published randomized trials comparing different strategies of managing conduction disturbances post-STEMI. Thus, the level of evidence for the recommendations in the table is C.

How to use the table

Example: 54-year-old man is admitted with an anterior STEMI and a narrow QRS on admission. On day 1 he develops a right bundle branch block (RBBB), with a PR interval of 0.28 seconds.

1. RBBB is an intra-ventricular conduction disturbance, so look at row "New BBB".
2. Find the column for "First Degree AV Block".
3. Find the "Action" and "Class" cells at the convergence.
4. Note that Observe and Atropine are Class III, not indicated; transcutaneous pacing (TC) is Class I. Temporary transvenous pacing (TV) is Class IIb.

(2 mg) doses of atropine have been used, transcutaneous or transvenous (preferably atrial) temporary pacing should be instituted. *(Level of Evidence: C)*

Pacing mode selection in STEMI patients

Class I

All patients who have an indication for permanent pacing after STEMI should be evaluated for ICD indications. *(Level of Evidence: C)*

Class IIa

1 It is reasonable to implant a permanent dual-chamber pacing system in STEMI patients who need permanent pacing and are in sinus rhythm. It is reasonable that patients in permanent atrial fibrillation or flutter receive a single chamber ventricular device. *(Level of Evidence: C)*

2 It is reasonable to evaluate all patients who have an indication for permanent pacing after STEMI for biventricular pacing (cardiac resynchronization therapy). *(Level of Evidence: C)*

G. Recurrent chest pain after STEMI

See Figure 3.7.

1. Pericarditis

Class I

1 Aspirin is recommended for treatment of pericarditis after STEMI. Doses as high as 650 mg orally (enteric) every 4 to 6 hours may be needed. *(Level of Evidence: B)*

2 Anticoagulation should be immediately discontinued if pericardial effusion develops or increases. *(Level of Evidence: C)*

Class IIa

For episodes of pericarditis after STEMI that are not adequately controlled with aspirin, it is reasonable to administer one or more of the following:

a. Colchicine 0.6 mg every 12 hours orally. *(Level of Evidence: B)*

b. Acetaminophen 500 mg orally every 6 hours. *(Level of Evidence: C)*

Class IIb

1 Nonsteroidal anti-inflammatory drugs may be considered for pain relief; however, they should not be used for extended periods because of their continuous effect on platelet function, an increased risk of myocardial scar thinning, and infarct expansion. *(Level of Evidence: B)* [17]

2 Corticosteroids might be considered only as a last resort in patients with pericarditis refractory to aspirin or nonsteroidal drugs. Although corticosteroids are effective for pain relief, their use is associated with an increased risk of scar thinning and myocardial rupture. *(Level of Evidence: C)*

Class III

Ibuprofen should not be used for pain relief because it blocks the antiplatelet effect of aspirin and can cause myocardial scar thinning and infarct expansion. *(Level of Evidence: B)*

2. Recurrent ischemia/infarction

Class I

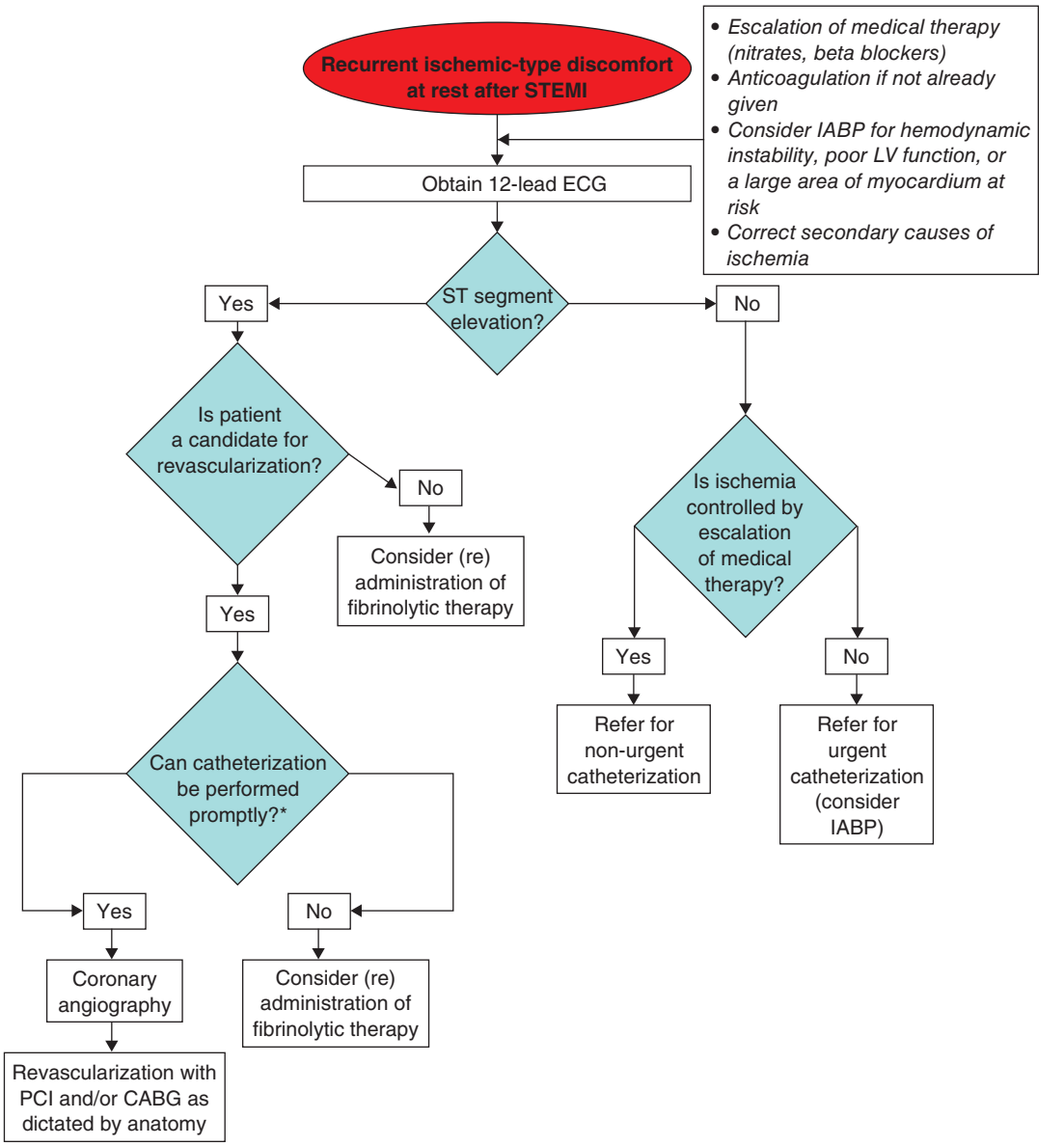
1 Patients with recurrent ischemic-type chest discomfort after initial reperfusion therapy for STEMI should undergo escalation of medical therapy with nitrates and beta-blockers to decrease myocardial oxygen demand and reduce ischemia. Intravenous anticoagulation should be initiated if not already accomplished. *(Level of Evidence: B)*

2 In addition to escalation of medical therapy, patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor LV function, or a large area of myocardium at risk should be referred urgently for cardiac catheterization and undergo revascularization as needed. Insertion of an IABP should also be considered. *(Level of Evidence: C)*

3 Patients with recurrent ischemic-type chest discomfort who are considered candidates for revascularization should undergo coronary arteriography and PCI or CABG as dictated by coronary anatomy. *(Level of Evidence: B)*

Class IIa

It is reasonable to (re)administer fibrinolytic therapy to patients with recurrent ST elevation and ischemic-type chest discomfort who are not considered candidates for revascularization or for whom coronary angiography and PCI cannot be rapidly (ideally within 60 minutes from the onset of recurrent discomfort) implemented. *(Level of Evidence: C)*



* Ideally within 60 minutes from the onset of recurrent discomfort

Fig. 3.7 Algorithm for management of recurrent ischemia/infarction after STEMI. IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery. Modified from: Braunwald E, Zipes D, Libby P. Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed. Philadelphia, PA: W.B. Saunders, 2001:1195.

Class III

Streptokinase should not be readministered to treat recurrent ischemia/infarction in patients who received a non-fibrin-specific fibrinolytic agent more than 5 days previously to treat the acute STEMI event. *(Level of Evidence: C)*

H. Other complications

1. Ischemic stroke

Class I

1 Neurological consultation should be obtained in STEMI patients who have an acute ischemic stroke. *(Level of Evidence: C)*

2 STEMI patients who have an acute ischemic stroke should be evaluated with echocardiography, neuroimaging, and vascular imaging studies to determine the cause of the stroke. *(Level of Evidence: C)*

3 STEMI patients with acute ischemic stroke and persistent atrial fibrillation should receive lifelong moderate intensity (international normalized ratio [INR] 2 to 3) warfarin therapy. *(Level of Evidence: A)*

4 STEMI patients with or without acute ischemic stroke who have a cardiac source of embolism (atrial fibrillation, mural thrombus, or akinetic segment) should receive moderate-intensity (INR 2 to 3) warfarin therapy (in addition to aspirin). The duration of warfarin therapy should be dictated by clinical circumstances (e.g., at least 3 months for patients with an LV mural thrombus or akinetic segment and indefinitely in patients with persistent atrial fibrillation). The patient should receive LMWH or UFH until adequately anticoagulated with warfarin. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to assess the risk of ischemic stroke in patients with STEMI. *(Level of Evidence: A)*

2 It is reasonable that STEMI patients with nonfatal acute ischemic stroke receive supportive care to minimize complications and maximize functional outcome. *(Level of Evidence: C)*

Class IIb

Carotid angioplasty/stenting, 4 to 6 weeks after ischemic stroke, might be considered in STEMI patients who have an acute ischemic stroke attributable to an internal carotid artery-origin stenosis of at least 50% and who have a high surgical risk of morbidity/mortality early after STEMI. *(Level of Evidence: C)*

2. DVT and pulmonary embolism

Class I

1 DVT or pulmonary embolism after STEMI should be treated with full-dose LMWH for a minimum of 5 days and until the patient is adequately anticoagulated with warfarin. Start warfarin concurrently with LMWH and titrate to INR of 2 to 3. *(Level of Evidence: A)*

2 Patients with CHF after STEMI who are hospitalized for prolonged periods, unable to ambulate, or considered at high risk for DVT and are not otherwise anticoagulated should receive low-dose heparin prophylaxis, preferably with LMWH. *(Level of Evidence: A)*

I. CABG surgery after STEMI

1. Timing of surgery

Class IIa

In patients who have had a STEMI, CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. Patients who have been stabilized (no ongoing ischemia, hemodynamic compromise, or life-threatening arrhythmia) after STEMI and who have incurred a significant fall in LV function should have their surgery delayed to allow myocardial recovery to occur. If critical anatomy exists, revascularization should be undertaken during the index hospitalization. *(Level of Evidence: B)*

2. Arterial grafting

Class I

An internal mammary artery graft to a significantly stenosed left anterior descending coronary artery should be used whenever possible in patients undergoing CABG after STEMI. *(Level of Evidence: B)*

3. CABG for recurrent ischemia after STEMI

Class I

Urgent CABG is indicated if the coronary angiogram reveals anatomy that is unsuitable for PCI. *(Level of Evidence: B)*

4. Elective CABG surgery after STEMI in patients with angina

Class I

1 CABG is recommended for patients with stable angina who have significant left main coronary artery stenosis. *(Level of Evidence: A)*

2 CABG is recommended for patients with stable angina who have left main equivalent disease: significant (at least 70%) stenosis of the proximal left anterior descending coronary artery and proximal left circumflex artery. *(Level of Evidence: A)*

3 CABG is recommended for patients with stable angina who have 3-vessel disease (survival benefit is greater when LVEF is less than 0.50). *(Level of Evidence: A)*

4 CABG is beneficial for patients with stable angina who have 1- or 2-vessel coronary disease without significant proximal left anterior descending coronary artery stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*
5 CABG is recommended in patients with stable angina who have 2-vessel disease with significant proximal left anterior descending coronary artery stenosis and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)*

5. CABG surgery after STEMI and antiplatelet agents

Class I

1 Aspirin should not be withheld before elective or nonelective CABG after STEMI. *(Level of Evidence: C)*
2 Aspirin (75 to 325 mg daily) should be prescribed as soon as possible (within 24 hours) after CABG unless contraindicated. *(Level of Evidence: B)*
3 In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days. *(Level of Evidence: B)*

J. Convalescence, discharge and post-MI care

See Figure 3.8.

1. Risk stratification at hospital discharge

a. Role of exercise testing

Class I

1 Exercise testing should be performed either in the hospital or early after discharge in STEMI patients not selected for cardiac catheterization and without high-risk features to assess the presence and extent of inducible ischemia. *(Level of Evidence: B)*
2 In patients with baseline abnormalities that compromise ECG interpretation, echocardiography or myocardial perfusion imaging should be added to standard exercise testing. *(Level of Evidence: B)*

Class IIb

Exercise testing might be considered before discharge of patients recovering from STEMI to guide the postdischarge exercise prescription or to evaluate the functional significance of a coronary lesion previously identified at angiography. *(Level of Evidence: C)*

Class III

1 Exercise testing should not be performed within 2 to 3 days of STEMI in patients who have not undergone successful reperfusion. *(Level of Evidence: C)*
2 Exercise testing should not be performed to evaluate patients with STEMI who have unstable postinfarction angina, decompensated CHF, life-threatening cardiac arrhythmias, noncardiac conditions that severely limit their ability to exercise, or other absolute contraindications to exercise testing. *(Level of Evidence: C)*
3 Exercise testing should not be used for risk stratification in patients with STEMI who have already been selected for cardiac catheterization. *(Level of Evidence: C)*

b. Role of echocardiography

Class I

1 Echocardiography should be used in patients with STEMI not undergoing LV angiography to assess baseline LV function, especially if the patient is hemodynamically unstable. *(Level of Evidence: C)*
2 Echocardiography should be used to evaluate patients with inferior STEMI, clinical instability, and clinical suspicion of RV infarction. (See ACC/AHA Guidelines for Clinical Application of Echocardiography.) *(Level of Evidence: C)*
3 Echocardiography should be used in patients with STEMI to evaluate suspected complications, including acute MR, cardiogenic shock, infarct expansion, VSR, intracardiac thrombus, and pericardial effusion. *(Level of Evidence: C)*
4 Stress echocardiography (or myocardial perfusion imaging) should be used in patients with STEMI for in-hospital or early post-discharge assessment for inducible ischemia when baseline abnormalities are expected to compromise ECG interpretation. *(Level of Evidence: C)*

Class IIa

1 Echocardiography is reasonable in patients with STEMI to re-evaluate ventricular function during recovery when results are used to guide therapy. *(Level of Evidence: C)*
2 Dobutamine echocardiography (or myocardial perfusion imaging) is reasonable in hemodynamically and electrically stable patients four or more days after STEMI to assess myocardial viability when

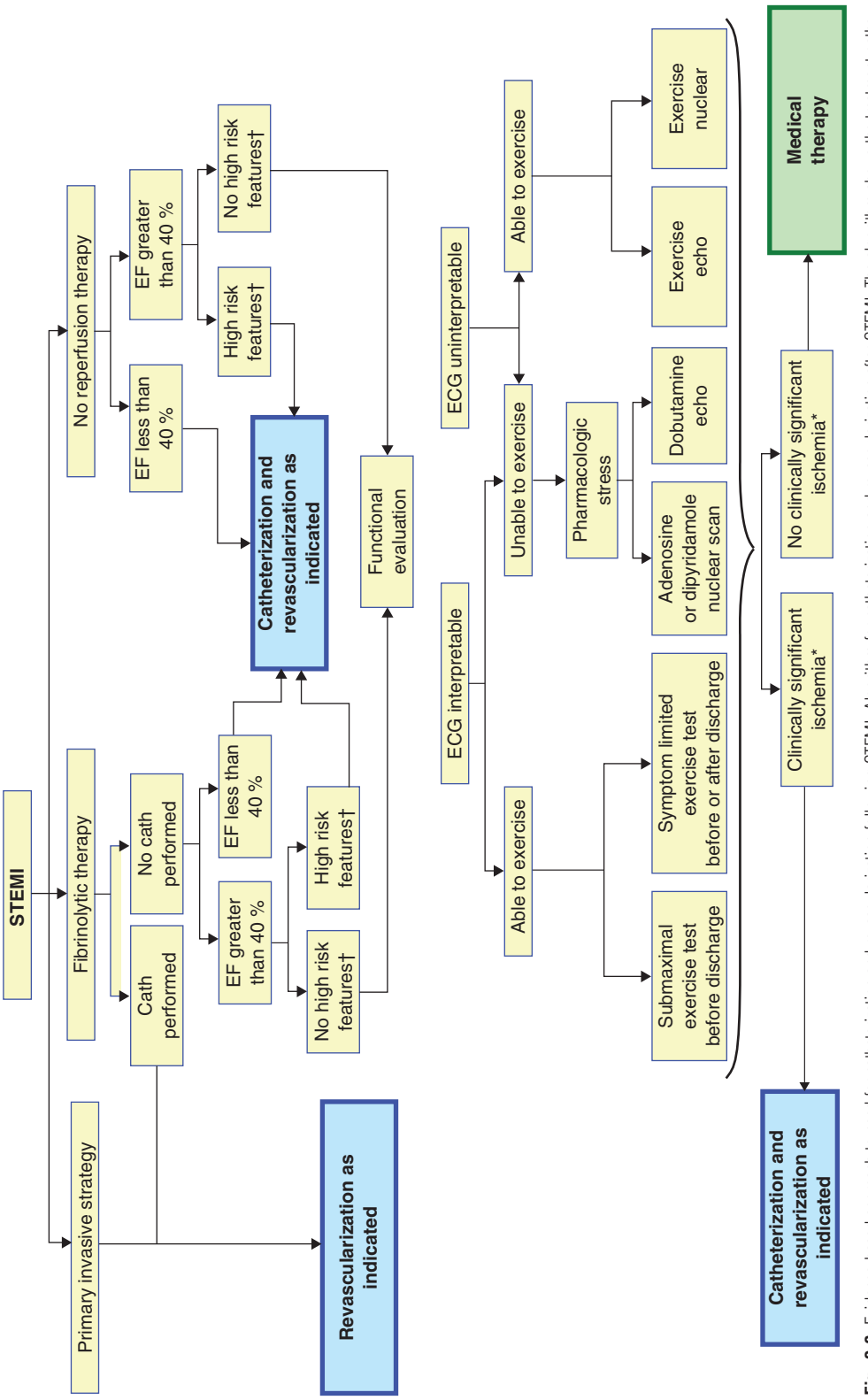


Fig. 3.8 Evidence-based approach to need for catheterization and revascularization following STEMI. Algorithm for catheterization and revascularization after STEMI. The algorithm shows the treatment paths for patients who initially undergo a primary invasive strategy, receive fibrinolytic therapy, or do not undergo reperfusion therapy for STEMI. Patients who have not undergone a primary invasive strategy and have no high risk features should undergo functional evaluation using one of the noninvasive tests shown. When clinically significant ischemia is detected, patients should undergo catheterization and revascularization as indicated; if no clinically significant ischemia is detected, medical therapy is prescribed post-STEMI.

*Please see the ACC/AHA Guidelines for the Management of Chronic Stable Angina (Table 23 of that Guideline) for further definition.

†Please see Table 3, Section 6.3.1.6.2., and Section 7.3 in the STEMI guideline for further discussion.

required to define the potential efficacy of revascularization. *(Level of Evidence: C)*

3 In STEMI patients who have not undergone contrast ventriculography, echocardiography is reasonable to assess ventricular function after revascularization. *(Level of Evidence: C)*

Class III

Echocardiography should not be used for early routine reevaluation in patients with STEMI in the absence of any change in clinical status or revascularization procedure. Reassessment of LV function 30 to 90 days later may be reasonable. *(Level of Evidence: C)*

c. Exercise myocardial perfusion imaging

Class I

Dipyridamole or adenosine stress perfusion nuclear scintigraphy or dobutamine echocardiography before or early after discharge should be used in patients with STEMI who are not undergoing cardiac catheterization to look for inducible ischemia in patients judged to be unable to exercise. *(Level of Evidence: B)*

Class IIa

Myocardial perfusion imaging or dobutamine echocardiography is reasonable in hemodynamically and electrically stable patients 4 to 10 days after STEMI to assess myocardial viability when required to define the potential efficacy of revascularization. *(Level of Evidence: C)*

d. LV function

Class I

LVEF should be measured in all STEMI patients. *(Level of Evidence: B)*

e. Invasive evaluation

See Figure 3.8.

Class I

1 Coronary arteriography should be performed in patients with spontaneous episodes of myocardial ischemia or episodes of myocardial ischemia provoked by minimal exertion during recovery from STEMI. *(Level of Evidence: A)*

2 Coronary arteriography should be performed for intermediate- or high-risk findings on noninvasive testing after STEMI (see Table 23 of the ACC/AHA Guidelines for the Management of Chronic Stable Angina). *(Level of Evidence: B)*

3 Coronary arteriography should be performed if the patient is sufficiently stable before definitive therapy of a mechanical complication of STEMI, such as acute MR, VSR, pseudoaneurysm, or LV aneurysm. *(Level of Evidence: B)*

4 Coronary arteriography should be performed in patients with persistent hemodynamic instability. *(Level of Evidence: B)*

5 Coronary arteriography should be performed in survivors of STEMI who had clinical heart failure during the acute episode but subsequently demonstrated well preserved LV function. *(Level of Evidence: C)*

Class IIa

1 It is reasonable to perform coronary arteriography when STEMI is suspected to have occurred by a mechanism other than thrombotic occlusion of an atherosclerotic plaque. This would include coronary embolism, certain metabolic or hematological diseases, or coronary artery spasm. *(Level of Evidence: C)*

2 Coronary arteriography is reasonable in STEMI patients with any of the following: diabetes mellitus, LVEF less than 0.40, CHF, prior revascularization, or life-threatening ventricular arrhythmias. *(Level of Evidence: C)*

Class IIb

Coronary arteriography may be considered as part of an invasive strategy for risk assessment after fibrinolytic therapy *(Level of Evidence: B)* or for patients not undergoing primary reperfusion. *(Level of Evidence: C)*

Class III

Coronary arteriography should not be performed in survivors of STEMI who are thought not to be candidates for coronary revascularization. *(Level of Evidence: A)*

f. Assessment of ventricular arrhythmias

Class IIb

Noninvasive assessment of the risk of ventricular arrhythmias may be considered (including signal-averaged ECG, 24-hour ambulatory monitoring,

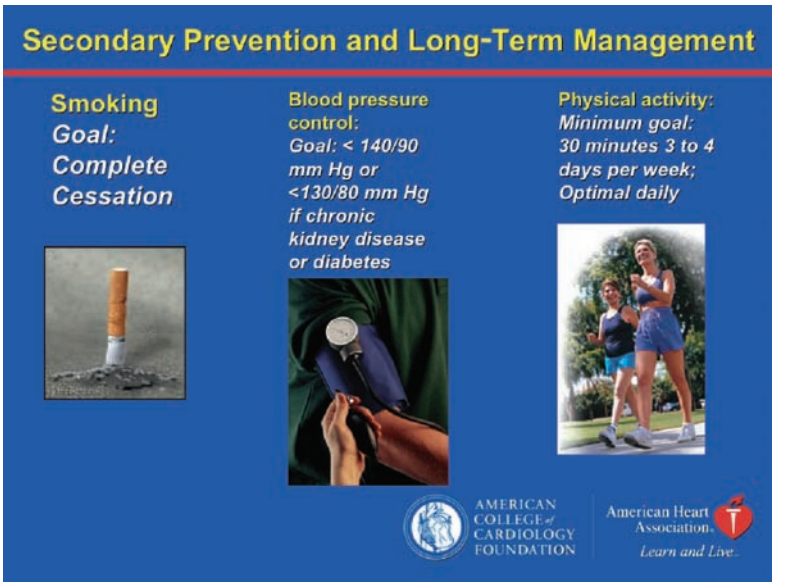


Fig. 3.9 Recommendations for secondary prevention after STEMI: smoking cessation, BP control, physical activity.

heart rate variability, micro T-wave alternans, and T-wave variability) in patients recovering from STEMI. *(Level of Evidence: B)*

K. Secondary prevention

See Figures 3.9, 3.10.

Class I

Patients who survive the acute phase of STEMI should have plans initiated for secondary prevention therapies. *(Level of Evidence: A)*

1. Patient education before discharge

Class I

1 Before hospital discharge, all STEMI patients should be educated about and actively involved in planning for adherence to the lifestyle changes and drug therapies that are important for the secondary prevention of cardiovascular disease. *(Level of Evidence: B)*

2 Post-STEMI patients and their family members should receive discharge instructions about recognizing acute cardiac symptoms and appropriate actions to take in response (i.e., calling 9-1-1 if symptoms are unimproved or worsening 5 minutes after onset, or if symptoms are unimproved or worsening 5 minutes after one sublingual nitroglycerin dose) to ensure early evaluation and treatment should symptoms recur. *(Level of Evidence: C)*

3 Family members of STEMI patients should be advised to learn about AEDs and CPR and be referred to a CPR training program. Ideally, such training programs would have a social support component targeting family members of high-risk patients. *(Level of Evidence: C)*

Contemporary recommendations for secondary prevention after STEMI can be found in the updated material contained in Chapter 5.

2. Antiplatelet therapy

See Figure 3.11.

Class I

1 A daily dose of aspirin 75 to 162 mg orally should be given indefinitely to patients recovering from STEMI. *(Level of Evidence: A)*

2 If true aspirin allergy is present, preferably clopidogrel (75 mg orally per day) or, alternatively, ticlopidine (250 mg orally twice daily) should be substituted. *(Level of Evidence: C)*

3 If true aspirin allergy is present, warfarin therapy with a target INR of 2.5 to 3.5 is a useful alternative to clopidogrel in patients less than 75 years of age

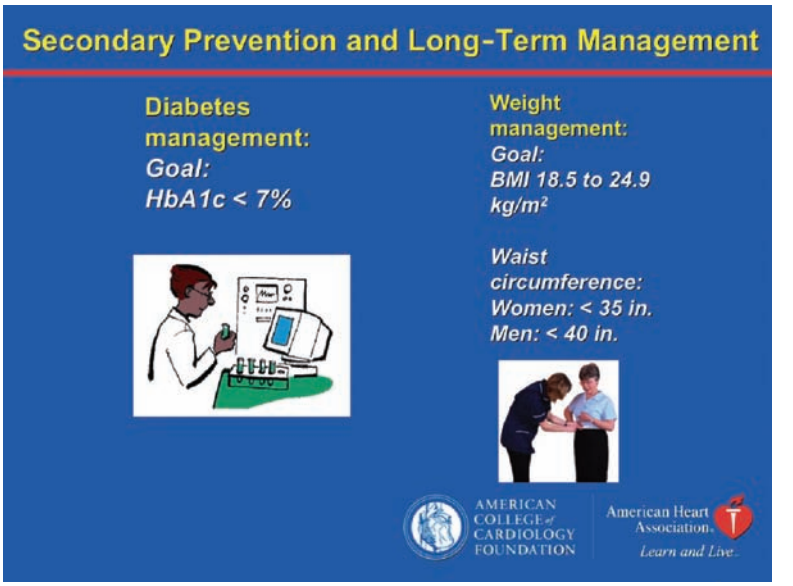


Fig. 3.10 Recommendations for secondary prevention after STEMI: diabetes management, weight management.

who are at low risk for bleeding and who can be monitored adequately for dose adjustment to maintain a target INR range. *(Level of Evidence: C)*

4 At the time of preparation for hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed and a stepped-care approach to pain management should be used for selection of treatments (Figure 3.12). Pain relief should begin with acetaminophen or aspirin, small doses of narcotics, or non-acetylated salicylates. *(Level of Evidence: C)* [17]

Class IIa

It is reasonable to use non-selective NSAIDs such as naproxen if initial therapy with acetaminophen, small doses of narcotics, or non-acetylated salicylates is insufficient. *(Level of Evidence: C)*

Class IIb

NSAIDs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations where intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs. In all cases, the lowest effective doses should be used for the shortest possible time. *(Level of Evidence: C)*

Class III

NSAIDs with increasing degrees of relative COX-2 selectivity should not be administered to STEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief. *(Level of Evidence: C)*

Long-term management

A. Psychosocial impact of STEMI

Class I

The psychosocial status of the patient should be evaluated, including inquiries regarding symptoms of depression, anxiety, or sleep disorders and the social support environment. *(Level of Evidence: C)*

Class IIa

Treatment with cognitive-behavioral therapy and selective serotonin reuptake inhibitors can be useful for STEMI patients with depression that occurs in

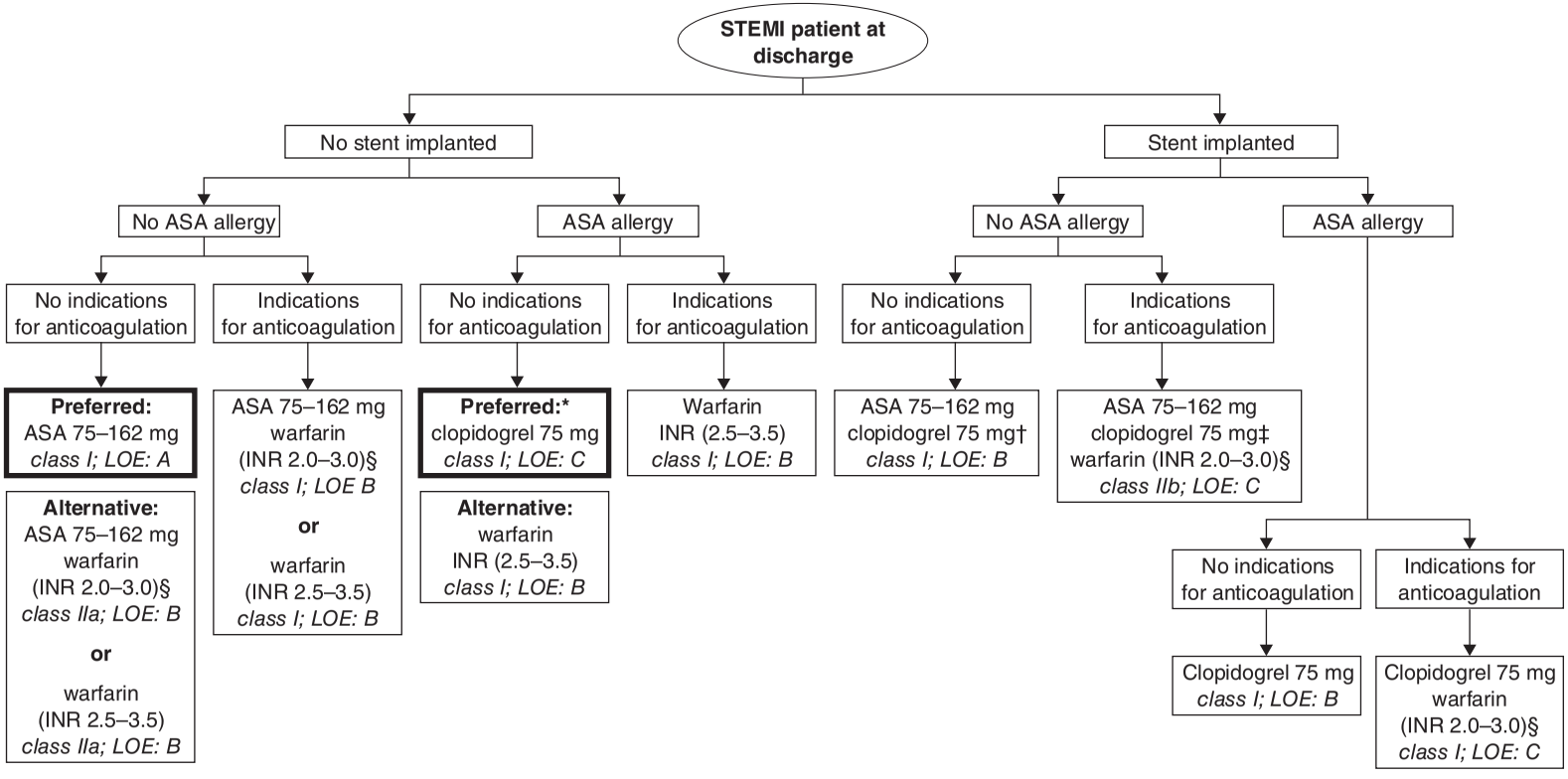


Fig. 3.11 Long-term antithrombotic therapy at hospital discharge after STEMI.

*Clopidogrel is preferred over warfarin due to increased risk of bleeding and low patient compliance in warfarin trials.

†For 12 months.

‡Discontinue clopidogrel 1 month after implantation of a bare metal stent or several months after implantation of a drug-eluting stent (3 months after sirolimus and 6 months after paclitaxel) because of the potential increased risk of bleeding with warfarin and two antiplatelet agents. Continue ASA and warfarin long term if warfarin is indicated for other reasons such as atrial fibrillation, LV thrombus, cerebral emboli, or extensive regional wall motion abnormality.

§An INR of 2.0–3.0 is acceptable with tight control, but the lower end of this range is preferable. The combination of antiplatelet therapy and warfarin may be considered in patients aged less than 75 years, with low bleeding risk, and who can be monitored reliably.

LOE, Level of evidence.

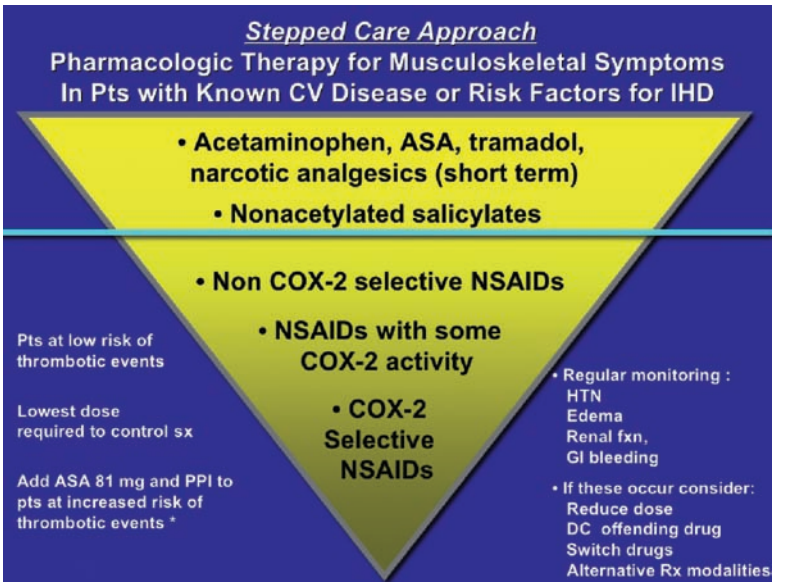


Fig. 3.12 In patients with known cardiovascular disease or who are at risk for ischemic heart disease, clinicians should use a stepped-care approach to pharmacological therapy, focusing on agents with the lowest reported risk of cardiovascular events and then progressing toward other agents with consideration of the risk–benefit balance at each step. Once the decision is made to prescribe an NSAID (below the horizontal line), additional considerations assume importance as illustrated by the recommendations at the bottom left and right of the diagram.

* Addition of ASA may not be sufficient protection against thrombotic events. ASA indicates aspirin; COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs; and PPI, proton pump inhibitors. Reproduced with permission from Antman *et al.* Circulation. 2007;115;1634.

the year after hospital discharge. *(Level of Evidence: A)*

B. Cardiac rehabilitation

Class IIa

Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. *(Level of Evidence: C)*

C. Follow-up visit with medical provider

Class I

1 A follow-up visit should delineate the presence or absence of cardiovascular symptoms and functional class. *(Level of Evidence: C)*

2 The patient's list of current medications should be reevaluated in a follow-up visit, and appropriate titration of ACE inhibitors, beta-blockers, and statins should be undertaken. *(Level of Evidence: C)*

3 The predischarge risk assessment and planned workup should be reviewed and continued. This should include a check of LV function and possibly Holter monitoring for those patients whose early post-STEMI ejection fraction was 0.31 to 0.40 or lower, in consideration of possible ICD use. *(Level of Evidence: C)*

4 The healthcare provider should review and emphasize the principles of secondary prevention with the patient and family members. *(Level of Evidence: C)*

5 The psychosocial status of the patient should be evaluated in follow-up, including inquiries regarding symptoms of depression, anxiety, or sleep disorders and the social support environment. *(Level of Evidence: C)*

6 In a follow-up visit, the healthcare provider should discuss in detail issues of physical activity, return to work, resumption of sexual activity, and travel, including driving and flying. The metabolic equivalent values for various activities are provided as a resource in Table 34 of the full-text guideline. *(Level of Evidence: C)*

7 Patients and their families should be asked if they are interested in CPR training after the patient is discharged from the hospital. *(Level of Evidence: C)*
8 Providers should actively review the following issues with patients and their families:

a. The patient's heart attack risk. *(Level of Evidence: C)*
b. How to recognize symptoms of STEMI. *(Level of Evidence: C)*
c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 minutes, despite feelings of uncertainty about the symptoms and fear of potential embarrassment. *(Level of Evidence: C)*
d. A plan for appropriate recognition and response to a potential acute cardiac event, including the phone number to access EMS, generally 9-1-1. *(Level of Evidence: C)*

9. Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. *(Level of Evidence: C)*

Comparison with ESC STEMI guidelines

The European Society of Cardiology (ESC) published guidelines for the management of STEMI patients in 2003 [18]. While the ESC document is shorter than the 2004 ACC/AHA document, it uses the same classification scheme for recommendations, and in general comes to the same conclusions as the ACC/AHA guidelines. Major emphasis is placed on timely reperfusion. There is greater experience with prehospital fibrinolysis in Europe than in the United States and a Class I recommendation is made to use prehospital fibrinolytic therapy if appropriate facilities exist. In general, it is recommended that fibrinolytic therapy be started within 90 minutes of the patient calling for medical treatment ("call to needle") or within 30 minutes of arrival at the hospital ("door to needle"). As with the ACC/AHA guidelines, primary PCI is the preferred therapeutic option when it can be performed within 90 minutes after the first medical contact and is implemented by an experienced team. In the 2003 ESC guidelines there is limited discussion about the pros and cons of planned PCI immediately after fibrinolytic therapy (facilitated PCI), since the more contemporary trials had not yet been reported or summarized in meta-analyses. It is likely that the planned update to the ESC STEMI guidelines will comment on the current recommendations about facilitated PCI as well as rescue PCI – these were important aspects of the 2007 focused update to the ACC/AHA STEMI Guidelines. The data on new

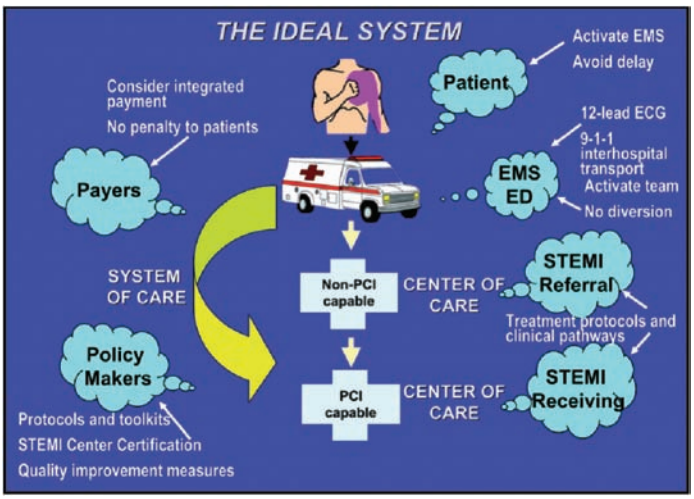


Fig. 3.13 Strategies for improving access to timely care for STEMI. Six major areas of consideration (patient, EMS/ED, STEMI referral hospital, STEMI receiving hospital, payors, policy makers) and specific issues are noted. The goal is to strive for an ideal system where there is an integrated delivery of healthcare for patients with STEMI, with appropriate clinical, administrative, and policy support. Reproduced from Jacobs *et al.* Circulation. 2007;116:217.

Table 3.7 Performance measures

Performance measure name	Measure description
1. Aspirin at arrival	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients without aspirin contraindications who received aspirin within 24 hours before or after hospital arrival.
2. Aspirin prescribed at discharge	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients without aspirin contraindications who are prescribed aspirin at hospital discharge.
3. Beta-blocker at arrival	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients without beta-blocker contraindications who received a beta-blocker within 24 hours after hospital arrival.
4. Beta-blockers prescribed at discharge	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients without beta-blocker contraindications who are prescribed a beta-blocker at hospital discharge.
5. LDL-cholesterol assessment	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients with documentation of low-density lipoprotein cholesterol (LDL-c) level in the hospital record or documentation that LDL-c testing was done during the hospital stay or is planned for after discharge.
6. Lipid-lowering therapy at discharge	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients with elevated low-density lipoprotein cholesterol (LDL-c ≥100 mg/dl or narrative equivalent) who are prescribed a lipid-lowering medication at hospital discharge.
7. ACEI or ARB for LVSD at discharge	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients with left ventricular systolic dysfunction (LVSD) and without both angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) contraindications who are prescribed an ACEI or ARB at hospital discharge.
8. Time to fibrinolytic therapy	Median time from arrival to administration of fibrinolytic therapy in patients with ST-segment elevation or left bundle branch block (LBBB) on the electrocardiogram (ECG) performed closest to hospital arrival time. Acute myocardial infarction (AMI-STEMI and LBBB only) patients receiving fibrinolytic therapy during the hospital stay and having a time from hospital arrival to fibrinolysis of 30 min or less.
9. Time to PCI	Median time from arrival to percutaneous coronary intervention (PCI) in patients with ST-segment elevation or left bundle branch block (LBBB) on the electrocardiogram (ECG) performed closest to arrival time. Acute myocardial infarction (AMI-STEMI and LBBB only) patients receiving percutaneous coronary intervention (PCI) during the hospital stay with a time from hospital arrival to PCI of 90 min or less.
10. Reperfusion therapy	Acute myocardial infarction (AMI-STEMI and LBBB only) patients with ST-segment elevation on the electrocardiogram (ECG) performed closest to arrival who receive fibrinolytic therapy or primary percutaneous coronary intervention (PCI).
11. Adult smoking cessation advice/counseling	Acute myocardial infarction (AMI-STEMI and NSTEMI) patients with a history of smoking cigarettes who are given smoking cessation advice or counseling during hospital stay.

LDL-c, low-density lipoprotein cholesterol; NSTEMI, non-ST-elevation MI; STEMI, ST-elevation MI.
From Krumholz HM, JACC. 2006;47:236.

anticoagulant approaches such as enoxaparin, fondaparinux, and bivalirudin as well as enhanced antiplatelet therapy with the combination of aspirin and clopidogrel were not available at the time of publication of the 2003 ESC Guidelines and plans are underway to provide updated recommendations regarding these treatments when the ESC STEMI Guidelines are updated.

Ongoing research efforts and future directions

Regardless of the mode of reperfusion, the overarching concept is to minimize total ischemic time, which is defined as the time from onset of symptoms of STEMI to initiation of reperfusion therapy. It is increasingly clear that two types of hospital system provide reperfusion therapy: those with percutaneous coronary intervention (PCI) capability and those without PCI capability. When PCI capability is available, the best outcomes are achieved by offering this strategy 24 hours per day, 7 days per week. The systems goal should be a first medical contact-to-balloon time within 90 minutes. There should be an ongoing program of outcomes analysis and periodic case review to identify process-of-care strategies that will continually improve time to treatment and facilitate rapid and appropriate treatment. A comprehensive effort in this regard is the AHA Mission: Lifeline program, a community-based national initiative to improve the quality of care and outcomes of patients with STEMI by improving health care system readiness and response to STEMI (Figure 3.13) [19]. The "Door-to-Balloon (D2B): An Alliance for Quality" campaign (www.d2balliance.org), launched by the ACC in collaboration with many organizations, including the AHA, aims to improve the timeliness of primary PCI. The goal is to increase the percentage of patients who receive timely primary PCI, with an emphasis on having at least 75% of patients treated within 90 minutes of presentation at the hospital, with a recommendation for the use of evidence-based strategies to reduce needless delays. The 75% goal was set in recognition that some patients have clinically relevant non-system-based delays that do not represent quality-of-care issues. In hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when the expected door-to-balloon time is within 90 minutes of first medical contact.

The STEMI Guidelines serve as the basis for performance measures, many of which are common to both STEMI and UA/NSTEMI patients (Table 3.7) [20].

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book these relevant AHA statements and guidelines were published: Hyperglycemia and Acute Coronary Syndrome, http://circ.ahajournals.org/cgi/content/full/117/12/1610; Management of Cocaine-Associated Chest Pain and Myocardial Infarction, http://circ.ahajournals.org/cgi/content/full/117/14/1897; Implementation and Integration of Prehospital ECGs into Systems of Care for Acute Coronary Syndromes, http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.190402.

4 Cardiac Rehabilitation and Secondary Prevention Programs

Mark A. Williams and Gary J. Balady

Introduction
Definition of cardiac rehabilitation/secondary prevention
Appropriate patients for cardiac rehabilitation/secondary prevention
CR/SP programming structure
Underutilization of cardiac rehabilitation/secondary prevention services
Core components of cardiac rehabilitation/secondary prevention programs
Exercise training intervention
Safety considerations
Effect on exercise capacity
Return to work
Effect on CVD prognosis
Cardioprotective mechanisms
Psychosocial interventions
Performance measures
Summary of the measures
Comparison with other national guidelines
Future research
Appendix A. Cardiac Rehabilitation/Secondary Prevention Performance Measurement Set A
Performance Measure A-1: Cardiac rehabilitation patient referral from an inpatient setting
Performance Measure A-2: Cardiac rehabilitation patient referral from an outpatient setting
Appendix B. Cardiac Rehabilitation/Secondary Prevention Performance Measurement Set B
Performance Measure B-1: Structure-based measurement set
Performance Measure B-2: Assessment of risk for adverse cardiovascular events
Performance Measure B-3: Individualized assessment and evaluation of modifiable cardiovascular risk factors, development of individualized interventions, and communication with other healthcare providers
Performance Measure B-3a: Individualized assessment of tobacco use
Performance Measure B-3b: Individualized assessment of blood pressure (BP) control
Performance Measure B-3c: Individualized assessment of optimal lipid control
Performance Measure B-3d: Individualized assessment of physical activity habits
Performance Measure B-3e: Individualized assessment of weight management
Performance Measure B-3f: Individualized assessment of the diagnosis of diabetes mellitus (DM) or impaired fasting glucose (IFG)
Performance Measure B-3g: Individualized assessment of the presence or absence of depression
Performance Measure B-3h: Individualized assessment of exercise capacity
Performance Measure B-3i: Individualized adherence to preventive medications
Performance Measure B-3j: Communication with healthcare providers
Performance Measure B-4: Monitor response to therapy and document program effectiveness

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Introduction

Cardiac Rehabilitation/Secondary Prevention (CR/SP) programming is an essential part of the contemporary care of patients with cardiovascular disease (CVD) [1–12] and is recommended as useful and effective (Class I) by the American Heart Association (AHA) and the American College of Cardiology (ACC) in the treatment of patients with coronary artery disease (CAD) [13–15] and chronic heart failure [16]. Consensus statements from the AHA [1], the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) [17], and the

Agency for Healthcare Policy and Research and others [1,12,18–27] conclude that cardiac rehabilitation programs should provided a multidisciplinary approach to overall cardiovascular risk reduction including but not limited to exercise training alone. As such CR/SP programs provide an important and efficient venue for delivery of preventive care, behavior medication, and the reduction of modifiable risk factors for CVD [1].

This chapter will review several recently published statements describing CR/SP program core components, program efficacy, and performance measures [1,28,29]. The chapter is intended to assist clinicians and cardiac rehabilitation program staff in the design and development of programs and to assist healthcare providers, insurers and policy makers, and consumers in the recognition of the comprehensive nature of such programs. It is not the intent of this chapter to promote a rote approach or homogeneity among programs but rather to foster a foundation of services on which each program can establish its own specific strengths and identity and effectively attain outcome goals for its target population. The AHA encourages clinicians to implement these program components and performance measures in order to provide for comprehensive cardiac rehabilitation/secondary prevention programs.

Definition of cardiac rehabilitation/secondary prevention

The term *cardiac rehabilitation/secondary prevention* refers to coordinated, multifaceted interventions designed to optimize cardiac patients' physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of the underlying atherosclerotic processes, thereby reducing morbidity and mortality [17]. CR is an integral component in the overall management of patients with CVD, whereby the patient plays a significant role in the successful outcomes of CR aimed at the secondary prevention of CVD events [2,3,12].

Appropriate patients for cardiac rehabilitation/secondary prevention

Candidates for CR/SP services historically were patients who had suffered a myocardial infarction (MI), undergone coronary artery bypass graft (CABG) surgery, or had been diagnosed with stable angina pectoris. However, more recently, candidacy has been broadened to include patients who have undergone percutaneous coronary intervention (PCI), heart transplantation, or heart valve replacement/repair [12]. Further, patients with stable chronic heart failure, peripheral arterial disease (PAD) with claudication, or other forms of CVD including cardiac surgical procedures, also may be eligible.

CR/SP programming structure

Cardiac rehabilitation/secondary prevention programs are generally divided into three main phases: (1) Inpatient CR (Phase 1 CR): a program that delivers preventive and rehabilitative services to hospitalized patients following an index CVD event, such as an MI/acute coronary syndrome; (2) Early outpatient CR (Phase 2 CR): a program generally beginning within 1–3 weeks post-hospitalization that delivers preventive and rehabilitative services, typically including electrocardiographic monitoring, to patients in the outpatient setting early after a CVD event, generally over the first 3 to 6 months post-hospitalization; (3) Long-term outpatient CR/SP (Phase 3/Phase 4): a program that provides long-term delivery of preventive and rehabilitative services for patients in the outpatient setting. The CR services are generally most beneficial when delivered soon after hospitalization. However, there are often clinical, social, and logistical reasons which delay enrollment in CR. For this reason, CR services may begin up to 6 to 12 months following a cardiac event. Because patients can be referred to CR at varying times following a CVD event, parties responsible for the referral of patients to CR include hospitals and healthcare systems as well as physician practices and other healthcare settings with primary responsibility for the care of patients after a CVD event.

Underutilization of cardiac rehabilitation/secondary prevention services

Unfortunately, CR/SP programs remain underused in the United States, with an estimated participation rate of only 10–20% of the >2 million eligible

patients per year [30]. Contributing to this poor level of utilization are potential barriers to participation including those which are patient-oriented (e.g., patient motivation), those that are provider-oriented (e.g., low patient referral rate, particularly of women, older adults, and ethnic minority patients), and still others related to societal barriers or the healthcare system (e.g., lack of insurance coverage or absence of a CR program) [30–32]. In addition, there is a lack of "visibility" and recognition by the public of the importance of cardiac rehabilitation services. It should be noted, however, that even though some persons may have significant patient- or provider-oriented barriers to CR referral, nearly all patients with CVD can benefit from at least some components of a comprehensive, secondary prevention CR program. To address these concerns effectively, alternative models to the traditional hospital- or community center-based setting for outpatient programs have been developed. These models include home-based and community-based group programs that use nurses or other non-physician healthcare providers, as well as electronic media programs as an alternative for providing risk-factor modification education and instruction for structured exercise [33–36].

Core components of cardiac rehabilitation/secondary prevention programs

All cardiac rehabilitation/secondary prevention programs should contain specific core components that aim to optimize cardiovascular risk reduction, foster healthy behaviors and compliance with these behaviors, reduce disability, and promote an active lifestyle for patients with cardiovascular disease. The AHA/AACVPR Core Components of Cardiac Rehabilitation/Secondary Prevention Programs [28] provide information on the evaluation, interventions, and expected outcomes for such programs in agreement with the 2006 update of the AHA/ACC secondary prevention guidelines [37], including baseline patient assessment, nutritional counseling, risk factor management (lipids, blood pressure, weight, diabetes mellitus, and smoking), psychosocial interventions, and physical activity counseling and exercise training (Table 4.1). Inherent in these

Table 4.1. Core components of cardiac rehabilitation/secondary prevention programs

Patient Assessment [17,36–39]

Evaluation

- Medical history: Review current and prior cardiovascular medical and surgical diagnoses and procedures (including assessment of left ventricular function); comorbidities (including peripheral arterial disease, cerebral vascular disease, pulmonary disease, kidney disease, diabetes mellitus, musculoskeletal and neuromuscular disorders, depression, and other pertinent diseases); symptoms of cardiovascular disease; medications (including dose, frequency, and compliance); date of most recent influenza vaccination; cardiovascular risk profile; and educational barriers and preferences. Refer to each core component of care for relevant assessment measures.
- Physical examination: Assess cardiopulmonary systems (including pulse rate and regularity, blood pressure, auscultation of heart and lungs, palpation and inspection of lower extremities for edema and presence of arterial pulses); post-cardiovascular procedure wound sites; orthopedic and neuromuscular status; and cognitive function. Refer to each core component for respective additional physical measures.
- Testing: Obtain resting 12-lead ECG; assess patient's perceived health-related quality of life or health status. Refer to each core component for additional specified tests.

Interventions

- Document the patient assessment information that reflects the patient's current status and guides the development and implementation of (1) a patient treatment plan that prioritizes goals and outlines intervention strategies for risk reduction, and (2) a discharge/follow-up plan that reflects progress toward goals and guides long-term secondary prevention plans.
- Interactively, communicate the treatment and follow-up plans with the patient and appropriate family members/domestic partners in collaboration with the primary healthcare provider.
- In concert with the primary care provider and/or cardiologist, ensure that the patient is taking appropriate doses of aspirin, clopidogrel, beta-blockers, lipid-lowering agents, and ACE inhibitors or angiotensin receptor blockers as per the ACC/AHA, and that the patient has had an annual influenza vaccination.

Table 4.1. *Continued*

Expected outcomes

- Patient Treatment Plan: Documented evidence of patient assessment and priority short-term (i.e., weeks–months) goals within the core components of care that guide intervention strategies. Discussion and provision of the initial and follow-up plans to the patient in collaboration with the primary healthcare provider.
- Outcome report: Documented evidence of patient outcomes within the core components of care that reflects progress toward goals, including whether the patient is taking appropriate doses of aspirin, clopidogrel, beta blockers, and ACE inhibitors or angiotensin receptor blockers as per the ACC/AHA, and whether the patient has had an annual influenza vaccination (and if not, documented evidence for why not), and identifies specific areas that require further intervention and monitoring.
- Discharge plan: Documented discharge plan summarizing long-term goals and strategies for success.

Nutritional counseling [40]

Evaluation

- Obtain estimates of total daily caloric intake and dietary content of saturated fat, trans fat, cholesterol, sodium, and nutrients.
- Assess eating habits, including fruit and vegetable, whole grain, and fish consumption; number of meals and snacks; frequency of dining out; and alcohol consumption.
- Determine target areas for nutrition intervention as outlined in the core components of weight, hypertension, diabetes, as well as heart failure, kidney disease, and other comorbidities.

Interventions

- Prescribe specific dietary modifications aiming to at least attain the saturated fat and cholesterol content limits of the Therapeutic Lifestyle Change diet. Individualize diet plan according to specific target areas as outlined in the core components of weight, hypertension, and diabetes (as outlined in this table), as well as heart failure and other comorbidities. Recommendations should be sensitive and relevant to cultural preferences.
- Educate and counsel patient (and appropriate family members/domestic partners) on dietary goals and how to attain them.
- Incorporate behavior change models and compliance strategies into counseling sessions.

Expected outcomes

- Patient adheres to prescribed diet.
- Patient understands basic principles of dietary content, such as calories, fat, cholesterol, and nutrients.
- A plan has been provided to address eating behavior problems.

Weight management [37,41,42]

Evaluation

- Measure weight, height, and waist circumference. Calculate body mass index (BMI).

Interventions

- In patients with BMI ≥25 kg/m^2 and/or waist >40 inches in men (102 cm) and >35 inches (88 cm) in women. BMI definitions for overweight and obesity may differ by race/ethnicity and region of the world. Relevant definitions, when available, should be respectively applied.
- Establish reasonable short-term and long-term weight goals individualized to the patient and his or her associated risk factors (e.g., reduce body weight by at least 5% and preferably by >10% at a rate of 1–2 lb/wk over a period of time up to 6 months).
- Develop a combined diet, physical activity/exercise, and behavioral program designed to reduce total caloric intake, maintain appropriate intake of nutrients and fiber, and increase energy expenditure. The exercise component should strive to include daily, longer distance/duration walking (e.g., 60–90 minutes).
- Aim for an energy deficit tailored to achieve weight goals (e.g., 500–1000 kcal/day).

Table 4.1. *Continued*

Expected outcomes

- Short-term: Continue to assess and modify interventions until progressive weight loss is achieved. Provide referral to specialized, validated nutrition weight loss programs if weight goals are not achieved.
- Long-term: Patient adheres to diet and physical activity/exercise program aimed toward attainment of established weight goal.

Blood pressure management [37,43]

Evaluation

- Measure seated resting blood pressure on ≥2 visits.
- Measure blood pressure in both arms at program entry.
- To rule out orthostatic hypotension, measure lying, seated, and standing blood pressure at program entry and after adjustments in antihypertensive drug therapy.
- Assess current treatment and compliance.
- Assess use of nonprescription drugs that may adversely affect blood pressure.

Interventions

- Provide and/or monitor therapy in concert with primary healthcare provider as follows:

If blood pressure is 120–139 mm Hg systolic or 80–89 mm Hg diastolic:

- Provide lifestyle modifications, including regular physical activity/exercise; weight management; moderate sodium restriction and increased consumption of fresh fruits, vegetables, and low-fat dairy products; alcohol moderation; and smoking cessation.
- Provide drug therapy for patients with chronic kidney disease, heart failure, or diabetes if blood pressure is ≥130/80 mmHg after lifestyle modification.

If blood pressure is ≥140 mmHg systolic or ≥90 mmHg diastolic:

- Provide lifestyle modification and drug therapy.

Expected outcomes

- Short-term: Continue to assess and modify intervention until normalization of blood pressure in pre-hypertensive patients; <140 mm Hg systolic and <90 mm Hg diastolic in hypertensive patients; <130 mm Hg systolic and <80 mm Hg diastolic in hypertensive patients with diabetes, heart failure, or chronic kidney disease.
- Long-term: Maintain blood pressure at goal levels.

Lipid management [37,40,44]

Evaluation

- Obtain fasting measures of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. In those patients with abnormal levels, obtain a detailed history to determine whether diet, drug, and/or other conditions that may affect lipid levels can be altered.
- Assess current treatment and compliance.
- Repeat lipid profiles at 4–6 weeks after hospitalization and at 2 months after initiation or change in lipid-lowering medications.
- Assess creatine kinase levels and liver function in patients taking lipid-lowering medications as recommended by NCEP.

Interventions

- Provide nutritional counseling consistent with the Therapeutic Lifestyle Change diet, such as the recommendation to add plant stanol/sterols and viscous fiber and the encouragement to consume more omega-3 fatty acids, as well as weight management counseling, as needed, in all patients. Add or intensify drug treatment in those with low-density lipoprotein ≥100 mg/dL; consider adding drug treatment in those with low-density lipoprotein ≥70 mg/dL.
- Provide interventions directed toward management of triglycerides to attain non-high-density lipoprotein cholesterol <130 mg/dL. These include nutritional counseling and weight management, exercise, smoking cessation, alcohol moderation, and drug therapy as per NCEP and AHA/ACC.
- Provide and/or monitor drug treatment in concert with primary healthcare provider.

Table 4.1. *Continued*

Expected outcomes

- Short-term: Continue to assess and modify intervention until low-density lipoprotein is <100 mg/dL (further reduction to a goal <70 mg/dL is considered reasonable) and non-high-density lipoprotein cholesterol <130 mg/dL (further reduction to a goal of <100 mg/dL is considered reasonable [36]).
- Long-term: Low-density lipoprotein cholesterol <100 mg/dL (further reduction to a goal <70 mg/dL is considered reasonable). Non-high-density lipoprotein cholesterol <130 mg/dL (further reduction to a goal of <100 mg/dL is considered reasonable).

Diabetes management [37,45,46]

Evaluation

From medical record review:

- Confirm presence or absence of diabetes in all patients.
- If a patient is known to be diabetic, identify history of complications such as findings related to heart disease; vascular disease; problems with eyes, kidneys, or feet; or autonomic or peripheral neuropathy.

From initial patient interview:

- Obtain history of signs/symptoms related to above complications and/or reports of episodes of hypoglycemia or hyperglycemia.
- Identify physician managing diabetic condition and prescribed treatment regimen, including:
  - Medications and extent of compliance.
  - Diet and extent of compliance.
  - Blood sugar monitoring method and extent of compliance.

Before starting exercise:

- Obtain latest fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c).
- Consider stratifying patient to high-risk category because of the greater likelihood of exercise-induced complications.

Interventions

- Educate patient and staff to be alert for signs/symptoms of hypoglycemia or hyperglycemia and provide appropriate assessment and interventions as per the American Diabetes Association.
- In those taking insulin or insulin secretogogues:
  - Avoid exercise at peak insulin times.
  - Advise that insulin be injected in abdomen, not muscle to be exercised.
  - Test blood sugar levels pre- and post-exercise at each session: if blood sugar value is <100 mg/dL, delay exercise and provide patient 15 g of carbohydrate; retest in 15 minutes; proceed if blood sugar value is ≥100 mg/dL; if blood sugar value is >300 mg/dL, patient may exercise if he or she feels well, is adequately hydrated, and blood and/or urine ketones are negative; otherwise, contact patient's physician for further treatment.
  - Encourage adequate hydration to avoid effects of fluid shifts on blood sugar levels.
  - Caution patient that blood sugar may continue to drop for 24–48 hours after exercise.
- In those treated with diet, metformin, alpha glucosidase inhibitors, and/or thiozolidinediones, without insulin or insulin secretogogues, test blood sugar levels prior to exercise for first 6–10 sessions to assess glycemic control; exercise is generally unlikely to cause hypoglycemia.

Education recommendations

- Teach and practice self-monitoring skills for use during unsupervised exercise.
- Refer to registered dietitian for medical nutrition therapy.
- Consider referral to certified diabetic educator for skill training, medication instruction, and support groups.

Expected outcomes

Short-term:

- Communicate with primary physician or endocrinologist about signs/symptoms and medication adjustments.
- Confirm patient's ability to recognize signs/symptoms, self-monitor blood sugar status, and self-manage activities.

Table 4.1. *Continued*

Long-term:
- Attain FPG levels of 90–130 mg/dL and HbA1c <7%.
- Minimize complications and reduce episodes of hypoglycemia or hyperglycemia at rest and/or with exercise.
- Maintain blood pressure at <130/<80 mm Hg.

Tobacco cessation [37,47]

Evaluation

Initial Encounter
- Ask the patient about his or her smoking status and use of other tobacco products. Document status as never smoked, former smoker, current smoker (includes those who have quit in the last 12 months because of the high probability of relapse). Specify both amount of smoking (cigarettes per day) and duration of smoking (number of years). Quantify use and type of other tobacco products. Question exposure to second-hand smoke at home and at work.
- Determine readiness to change by asking every smoker/tobacco user if he or she is now ready to quit.
- Assess for psychosocial factors that may impede success.

Ongoing contact
- Update status at each visit during first 2 weeks of cessation, periodically thereafter.

Interventions
- When readiness to change is not expressed, provide a brief motivational message containing the "5 Rs": Relevance, Risks, Rewards, Roadblocks, and Repetition.
- When readiness to change is confirmed, continue with the "5 As": Ask, Advise, Assess, Assist, and Arrange. Assist the smoker/tobacco user to set a quit date, and select appropriate treatment strategies (preparation):

Minimal (brief)
- Individual education and counseling by program staff supplemented by self-teaching materials.
- Social support provided by physician, program staff, family and/or domestic partner; identify other smokers in the house; discuss how to engage them in the patient's cessation efforts.
- Relapse prevention: problem solving, anticipated threats, practice scenarios.

Optimal (intense)
- Longer individual counseling or group involvement.
- Pharmacological support (in concert with primary physician): nicotine replacement therapy, bupropion hydrochloride.
- Supplemental strategies if desired (e.g., acupuncture, hypnosis).
- If patient has recently quit, emphasize relapse prevention skills.
- Urge avoidance of exposure to second-hand smoke at work and home.

Expected outcomes
- Patients who continue to smoke upon enrollment are subsequently more likely to drop out of cardiac rehabilitation/secondary prevention programs.
- Short-term: Patient will demonstrate readiness to change by initially expressing decision to quit and selecting a quit date. Subsequently, patient will quit smoking and all tobacco use and adhere to pharmacological therapy (if prescribed) while practicing relapse prevention strategies; patient will resume cessation plan as quickly as possible when temporary relapse occurs.
- Long-term: Complete abstinence from smoking and use of all tobacco products for at least 12 months (maintenance) from quit date. No exposure to environmental tobacco smoke at work and home.

Psychosocial management [2,17]

Evaluation
- Identify psychological distress as indicated by clinically significant levels of depression, anxiety, anger or hostility, social isolation, marital/family distress, sexual dysfunction/adjustment, and substance abuse (alcohol or other psychotropic agents), using interview and/or standardized measurement tools.
- Identify use of psychotropic medications.

Table 4.1. *Continued*

Interventions

- Offer individual and/or small group education and counseling on adjustment to heart disease, stress management, and health-related lifestyle change. When possible, include family members, domestic partners, and/or significant others in such sessions.
- Develop supportive rehabilitation environment and community resources to enhance the patient's and the family's level of social support.
- Teach and support self-help strategies.
- In concert with primary healthcare provider, refer patients experiencing clinically significant psychosocial distress to appropriate mental health specialists for further evaluation and treatment.

Expected outcomes

- Emotional well-being is indicated by the absence of clinically significant psychological distress, social isolation, or drug dependency.
- Patient demonstrates responsibility for health-related behavior change, relaxation, and other stress management skills; ability to obtain effective social support; compliance with psychotropic medications if prescribed; and reduction or elimination of alcohol, tobacco, caffeine, or other nonprescription psychoactive drugs.
- Arrange for ongoing management if important psychosocial issues are present.

Physical activity counseling [37,48–50]

Evaluation

- Assess current physical activity level (e.g., by questionnaire, pedometer) and determine domestic, occupational, and recreational needs.
- Evaluate activities relevant to age, gender, and daily life, such as driving, sexual activity, sports, gardening, and household tasks.
- Assess readiness to change behavior, self-confidence, barriers to increased physical activity, and social support in making positive changes.

Interventions

- Provide advice, support, and counseling about physical activity needs on initial evaluation and in follow-up. Target exercise program to meet individual needs (see Exercise Training section of table). Provide educational materials as part of counseling efforts. Consider exercise tolerance or simulated work testing for patients with heavy labor jobs.
- Consistently encourage patients to accumulate 30–60 minutes per day of moderate-intensity physical activity on ≥5 (preferably most) days of the week. Explore daily schedules to suggest how to incorporate increased activity into usual routine (e.g., parking farther away from entrances, walking ≥2 flights of stairs, and walking during lunch break).
- Advise low-impact aerobic activity to minimize risk of musculoskeletal injury. Recommend gradual increases in the volume of physical activity over time.
- Caution patients to avoid performing unaccustomed vigorous physical activity (e.g., racquet sports and manual snow removal). Reassess the patient's ability to perform such activities as exercise training program progresses.

Expected outcomes

- Patient shows increased participation in domestic, occupational, and recreational activities.
- Patient shows improved psychosocial well-being, reduction in stress, facilitation of functional independence, prevention of disability, and enhancement of opportunities for independent self-care to achieve recommended goals.
- Patient shows improved aerobic fitness and body composition and lessens coronary risk factors (particularly for the sedentary patient who has adopted a lifestyle approach to regular physical activity).

Exercise training [17,48–51]

Evaluation

- Symptom-limited exercise testing prior to participation in an exercise-based cardiac rehabilitation program is strongly recommended. The evaluation may be repeated as changes in clinical condition warrant. Test parameters should include assessment of heart rate and rhythm, signs, symptoms, ST-segment changes, hemodynamics, perceived exertion, and exercise capacity.

Table 4.1. *Continued*

- On the basis of patient assessment and the exercise test if performed, risk stratify the patient to determine the level of supervision and monitoring required during exercise training. Use risk stratification schema as recommended by the AHA and the AACVPR.

Interventions

- Develop an individualized exercise prescription for aerobic and resistance training that is based on evaluation findings, risk stratification, comorbidities (e.g., peripheral arterial disease and musculoskeletal conditions), and patient and program goals. The exercise regimen should be reviewed by the program medical director or referring physician, modified if necessary, and approved. Exercise prescription should specify frequency (F), intensity (I), duration (D), modalities (M), and progression (P).
- For aerobic exercise: F = 3–5 days/wk; I = 50–80% of exercise capacity; D = 20–60 minutes; and M = walking, treadmill, cycling, rowing, stair climbing, arm/leg ergometry, and others using continuous or interval training as appropriate.
- For resistance exercise: F = 2–3 days/wk; I = 10–15 repetitions per set to moderate fatigue; D = 1–3 sets of 8–10 different upper and lower body exercises; and M = calisthenics, elastic bands, cuff/hand weights, dumbbells, free weights, wall pulleys, or weight machines.
- Include warm-up, cool-down, and flexibility exercises in each exercise session.
- Provide progressive updates to the exercise prescription and modify further if clinical status changes.
- Supplement the formal exercise regimen with activity guidelines as outlined in the Physical Activity Counseling section of this table.

Expected outcomes

- Patient understands safety issues during exercise, including warning signs/symptoms.
- Patient achieves increased cardiorespiratory fitness and enhanced flexibility, muscular endurance, and strength.
- Patient achieves reduced symptoms, attenuated physiologic responses to physical challenges, and improved psychosocial well-being.
- Patient achieves reduced global cardiovascular risk and mortality resulting from an overall program of cardiac rehabilitation/secondary prevention that includes exercise training.

recommendations is the understanding that successful risk factor modification and maintenance of a physically active lifestyle is a lifelong process. Incorporation of strategies to optimize patient adherence to lifestyle and pharmacological therapies is integral to sustaining benefits. It is essential that each of these interventions is performed in concert with the patient's primary care provider and/or cardiologist, who will subsequently supervise and refine these interventions over the long term [38].

Exercise training intervention

Guidelines for prescribing aerobic and resistance exercise for patients with CHD are available elsewhere [17,28,37,52–55]. Specific activity recommendations also are available for women [56], older adults [57], patients with chronic heart failure and heart transplants [50], stroke survivors [58], and patients with claudication induced by peripheral arterial disease [59].

Safety considerations

The relative safety of medically supervised, physician-directed, CR/SP exercise programs is well established. The occurrence of major cardiovascular events during supervised exercise in contemporary programs ranges from 1/50,000 to 1/120,000 patient-hours of exercise, with only two fatalities reported per 1.5 million patient-hours of exercise [60]. Contemporary risk stratification procedures for the management of coronary heart disease (CHD) help to identify patients who are at increased risk for exercise-related cardiovascular events and who may require more intensive cardiac monitoring in addition to the medical supervision provided for all cardiac rehabilitation program participants [17].

Effect on exercise capacity

Exercise training and regular daily physical activities (e.g., working around the house and yard, climbing stairs, walking or cycling for transportation or recreation) are essential for improving a cardiac patient's physical fitness. Supervised CR exercise for 3 to 6 months generally is reported to increase a patient's peak oxygen uptake by 11% to 36%, with the greatest improvement in the most deconditioned individuals [2,30]. Improved fitness enhances a patient's quality of life and even can help older

adults to live independently [61]. Improved physical fitness is also associated with reductions in submaximal heart rate, systolic blood pressure, and rate-pressure product (RPP), thereby decreasing myocardial oxygen requirements during moderate-to-vigorous activities of daily living. Improved fitness allows patients with advanced CAD who ordinarily experience myocardial ischemia during physical exertion to perform such tasks at a higher intensity level before reaching an ischemic electrocardiogram or anginal threshold. Furthermore, improvement in muscular strength after resistance training also can decrease RPP (and associated myocardial demands) during daily activities, such as carrying groceries or lifting moderate to heavy objects [54]. Improvement in cardiorespiratory endurance is also associated with a significant reduction in subsequent cardiovascular fatal and nonfatal events independent of other risk factors [62–65].

Return to work

Although exercise training improves functional capacity and associated reduction in cardiorespiratory symptoms which should enhance a cardiac patient's ability to perform most job-related physical tasks, factors unrelated to physical fitness appear to have a greater influence on whether a patient returns to work after a cardiac event [66]. These factors include socioeconomic and worksite-related issues, and previous employment status. The educational and vocational counseling components of CR programs should further improve the ability of a patient to return to work.

Effect on CVD prognosis

CR/SP services are beneficial for patients with established CVD. These benefits include improved processes of care and risk-factor profiles that are closely linked to subsequent mortality and morbidity. Pooled data from randomized clinical trials of CR demonstrate a mortality benefit of approximately 20% to 25% and a trend towards reduction in nonfatal recurrent MI [2–11], despite the limitations inherent in the various analyses, including the paucity of data for women, older people, ethnic minorities, and patients who underwent revascularization procedures or who had other types of cardiac conditions. Major technological and biotechnical advances in the management of patients with CHD during the 1990s and early 21st century raise further questions about the relevance of findings from these earlier meta-analyses to the independent effects of contemporary CR/SP on morbidity, mortality, and other outcome variables. Few data were provided in these studies on the use of acute thrombolytic therapy and adjunctive cardioprotective drugs. Furthermore, quality of life was assessed, via a variety of measures, in only 25% of the clinical trials, and similar improvement was noted in both the exercise-based rehabilitation and control groups.

Cardioprotective mechanisms

Exercise training, as part of a comprehensive CR/SP program, has been shown to slow the progression or partially reduce the severity of coronary atherosclerosis [67–69]. Multiple factors directly or indirectly appear to contribute to this anti-atherosclerotic effect including improved endothelial function [70–73] and anti-inflammatory effects [74–76] although these observations require confirmation, especially in patients with CAD.

In addition, exercise training and regular physical activity can result in moderate losses in body weight and adiposity [77,78], promote decreases in blood pressure [79,80], improve serum triglycerides and high-density lipoprotein cholesterol [81–84], and insulin sensitivity and glucose homeostasis [85]. Along with modest weight reduction, these latter improvements have been shown to reduce the risk of type 2 diabetes mellitus in individuals with glucose intolerance [86,87]. Thus, aerobic exercise can favorably modify all of the components of the metabolic syndrome [88] and serve as a first-line therapy to combat this complex constellation of risk factors for type 2 diabetes mellitus and CVD [89].

Endurance exercise training also has potential anti-ischemic effects by reducing myocardial ischemia in patients with advanced CHD by decreasing myocardial oxygen demands during physical exertion [48], increasing coronary flow by improving coronary artery compliance or elasticity [90,91] and endothelium-dependent vasodilatation [76], and by increasing the luminal area of conduit vessels through remodeling or arteriogenesis and myocardial capillary density by angiogenesis [92]. Furthermore, in the presence of advanced CAD, exercise training has been shown to induce ischemic preconditioning of the myocardium and potentially

decrease the risk of sudden cardiac death due to ventricular tachyarrhythmias [93,94].

Exercise training appears to alter hemostatic effects, which can reduce the risk of a thrombotic occlusion of a coronary artery after the disruption of a vulnerable plaque. These antithrombotic effects include increased plasma volume, reduced blood viscosity, decreased platelet aggregation, and enhanced thrombolytic ability [95,96]. Some studies also have shown that exercise training may reduce plasma levels of fibrinogen [96].

Psychosocial interventions

Psychosocial dysfunction is common in patients participating in CR. These problems include depression, anger, anxiety disorders, and social isolation. Observational studies have demonstrated associations between psychosocial disorders and the risk of initial or recurrent cardiovascular events [97]. However, a large randomized multicenter trial reported that cases of depression and social isolation improved similarly in both the intervention and control groups [98] with no improvement in event-free survival. Nevertheless, even if psychosocial interventions ultimately are shown not to alter the prognosis of CHD patients, they remain an integral part of cardiac rehabilitation services to improve the psychological well-being and quality of life of cardiac patients.

Performance measures

Using a previously published methodology [15,99], the AHA, in conjunction with the AACVPR and the ACC, has addressed performance measures for the referral of eligible patients to a CR program and the delivery of CR services through multidisciplinary CR programs, focusing on processes of care that have been documented to help improve patient outcomes (Appendices A and B) [29]. The purpose of these performance measure sets is to help improve the delivery of CR in order to reduce cardiovascular mortality and morbidity and optimize health in persons with CVD, including acute MI, CABG surgery, PCI, stable angina pectoris, and heart transplant or heart valve surgery.

The rationale for developing and implementing performance measure sets for referral to and delivery of CR services was based on several key factors:

- Despite the known benefits of CR and the widespread endorsement of its use, CR is vastly underutilized [104–106]. Reasons for this gap in CR participation are numerous, but the most critical and potentially most correctable reasons revolve around obstacles in the initial referral of patients to CR programs. These obstacles can be reduced through the systematic adoption of standing orders and other similar tools for CR referral for appropriate hospitalized patients [107]. Furthermore, physician accountability associated with the use of these performance measures may lead to innovative approaches to improve referral rates and improve the outcome of patients with CVD.
- The core components for CR have been published [28] (Table 4.1) and systems for CR program certification exist [108]. However, since certification is not required in most instances for CR program operation or for reimbursement purposes, CR program certification is obtained by a relatively small portion of CR programs in the United States [109].
- There is a need to reduce the gap in delivery of CR services to persons with CVD. Improvement in CR delivery will require better approaches in the referral to, enrollment in, and completion of programs in CR. It is anticipated that the implementation of CR performance measure sets will stimulate changes in the clinical practice of preventive and rehabilitative care for persons with CVD. The performance measures are designed to help healthcare groups identify potentially correctable and actionable sources of suboptimal clinical care such as structure- and process-based gaps in CR services.

1 Structure-based measures quantify the infrastructure from which CR is provided and are based upon the provision of appropriate personnel and equipment to satisfy high quality standards of care for CR services. For example, a structure-based performance measure for a CR program is one that specifies that a CR program has appropriate personnel and equipment to provide rapid care in medical emergencies that may occur during CR program sessions.

2 Process-based measures quantify specific aspects of care and are designed to capture all relevant dimensions of CR care. For example, a process-based performance measure for a CR program is one that specifies that all patients in a CR program

undergo comprehensive, standardized assessment of their cardiovascular risk factors upon entry to the CR program.

It should also be noted that the Cardiac Rehabilitation/Secondary Prevention Performance Measurement Sets have been designed for three different geographical settings of care: (1) the hospital; (2) the physician's office; and (3) the CR program settings. Staff members within each of these areas who help provide care to persons with CVD are held accountable for the various aspects of CR services (referral to, enrollment in, and delivery of CR services).

Summary of the measures

Performance measures focused on those groups of patients with the most current scientific evidence and other supporting evidence for benefits from CR. Because of limitations in space in the present document, the Performance Measurement Sets in their entirety are not included here. The specifics of the measurement process including rationale for doing so, challenges to implementation of the measures, and corresponding guidelines and clinical recommendations references are included in the original publication as well as examples of data collection instruments tools that may be of help in applying the Cardiac Rehabilitation/Secondary Prevention Performance Measurement Sets. These tools are given as examples and not as endorsed instruments. Healthcare systems and providers are encouraged to develop and implement systematic tools that are most appropriate and most effective for their particular setting and patient population groups.

The Cardiac Rehabilitation/Secondary Prevention Performance Measurement Set A (Appendix A) is based on two criteria for the appropriate referral of patients to an early outpatient CR program:

1 All hospitalized patients with a qualifying CVD event are referred to an early outpatient CR program prior to hospital discharge; and
2 All outpatients with a qualifying diagnosis within the past year who have not already participated in an early outpatient CR program associated with this qualifying diagnosis are referred to an early outpatient CR program by their healthcare provider. Patients with new qualifying diagnoses may be eligible for additional early outpatient programming even though they have participated in such programming within the previous 12 months.

It should be noted that the healthcare system and its providers who care for patients during and/or after CVD events are accountable for these performance measures. Physicians or other healthcare providers who see patients with CVD but who do not have a primary role in managing their CVD are not accountable for meeting these criteria. For example, an ophthalmologist who is performing an annual retinal exam on a diabetic patient in the year after an MI would not be responsible for referring the patient to a CR program.

The second set of performance measures included in the Cardiac Rehabilitation/Secondary Prevention Performance Measurement Sets Performance Measurement Set B (Appendix B) relates to the optimal structure and processes of care for CR programs themselves and is described in the next section. The unit of analysis for the Cardiac Rehabilitation/Secondary Prevention Performance Measurement Set B is the healthcare system's CR program(s). Therefore, the responsible parties for the performance of early outpatient CR services include members of the CR program staff including the medical director, nurses, exercise specialists, cardiovascular administrators, and other members of the CR team. The Cardiac Rehabilitation/Secondary Prevention Performance Measurement Set B is intended to be used prospectively to review a program's internal procedures with the ultimate goal of enhancing the quality improvement process.

As more evidence becomes available for the benefits of CR in these patient groups, they will be included in future iterations of the Cardiac Rehabilitation/Secondary Prevention Performance Measurement Sets. To be effective, the recommendations of the Performance Measure statement will need to be adapted, adopted, and implemented by healthcare systems, healthcare providers, health insurance carriers, chronic disease management organizations, and other groups in the healthcare field that have responsibility for the delivery of care to persons with CVD. Such strategies should be part of an overall systems-based approach to minimize inappropriate gaps and variation in patient care, optimize delivery of health-promoting services, and improve patient-centered health outcomes.

Comparison with other national guidelines

Many individual countries throughout the world have published guidelines for cardiac rehabilitation/secondary prevention programs. These include those from Canada, several countries in Europe, Australia, and South Africa. While each of these may differ slightly, the overriding theme is that the comprehensive nature of cardiac rehabilitation extends beyond exercise training alone. Emphasis is placed on the importance of the identification and treatment of modifiable risk factors for cardiovascular disease. The AHA/AACVPR statements and guidelines for cardiac rehabilitation/secondary prevention programs are derived in concert with the other national guidelines that address prevention, including the JNC 7 [43], NCEP-ATP3 [40], and the AHA/ACC Secondary Prevention Guidelines [37]. The remarkable pace of scientific discovery challenges the provision of recommendations that reflect the most current science. Accordingly, the guidelines on cardiac rehabilitation/secondary prevention programs are consistent with the best scientific knowledge base available at the time of the writing of the document, and may at times provide treatment targets and strategies that differ from other prevention-focused guidelines that were published several years earlier. It is therefore both reasonable and appropriate that medical directors of cardiac rehabilitation/secondary prevention programs remain keenly aware of advances in the broad field of prevention, and implement programmatic changes relative to the most recent scientific consensus regarding a particular area (e.g., lipid management).

The recently published European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [110] promote the use of global risk scores, and establish treatment targets that are nearly identical to those of the American guidelines. They emphasize the importance of behavior and behavioral change strategies that foster the adoption and maintenance of healthy lifestyles, as this is fundamental to the attainment of individual risk factor modification and treatment goals.

Future research

As cardiac rehabilitation/secondary prevention programs encompass a very broad field that ranges from management of individual risk factors to behavior/adherence strategies, there are many opportunities for future research. Some specific areas are as follows [1]:

1 Evaluations to determine the effectiveness and safety of a variety of approaches designed to increase patient referrals, accessibility, and delivery of cardiac rehabilitation and secondary prevention services and to promote adherence to program components.
2 Comparisons of the cost-effectiveness of traditional supervised programs versus home-based exercise and educational services with regard to improving functional capacity, self-efficacy, independent living, risk factor modification, long-term compliance, rehospitalization rates, and quality of life.
3 Evaluation of the contributions of endurance and resistance exercise for the modification of risk factors and their effects on pathophysiological mechanisms involved in atherogenesis, myocardial ischemia, coronary thrombosis, and ventricular tachyarrhythmias.
4 Randomized trials to better define the role of exercise therapy for safely improving functional capacity, reducing cardiovascular symptoms, and enhancing the quality of life among specific subgroups of patients with cardiovascular disease, particularly older, female, and ethnic minority patients.
5 Feasibility of definitive randomized multicenter clinical trials to assess the independent contribution of exercise training to the morbidity and mortality of patients after myocardial infarction or coronary artery revascularization procedures and of patients with stable angina pectoris or silent myocardial ischemia. These trials should include older, female, and ethnic minority patients.
6 Studies to clarify the independent and additive benefits of lifestyle modification (i.e. beyond coronary revascularization and effective pharmacotherapies) individually or in combination with other interventions in preventing recurrent cardiovascular events.
7 Evaluation of the use of cardiac rehabilitation programs as centers for intensive lifestyle management for weight loss, physical activity, nutrition, and psychosocial support for people with additional chronic medical conditions, such as type 2 diabetes mellitus, the metabolic syndrome, and other insulin resistant states.

There are numerous ongoing trials that address specific risk factors for cardiovascular disease. Information regarding these can be found at www.clinicaltrials.gov. Several other trials are particularly directed toward cardiac rehabilitation. Perhaps the most important of these is the Heart Failure ACTION trial, which is the largest randomized trial of exercise training ever conducted. This is a multicenter randomized controlled trial funded by the National Institutes of Health aimed at evaluating the safety and efficacy of exercise training plus enhanced evidence based care compared with enhanced evidence-based care alone in patients with Class II–IV heart failure. The primary outcomes of this study are all-cause mortality and frequency of hospitalizations for heart failure. There are many secondary outcome analyses and substudies from this trial that will provide additional important information [110]. Selected other cardiac rehabilitation trials are listed below with their NCT identification number. These can be accessed at www.clinicaltrials.gov.

- Anti-Arrhythmic Effects of Exercise After an Implantable Cardioverter Defibrillator (ICD). NCT00522340
- Percutaneous Coronary Angioplasty Compared With Exercise Training in Symptomatic Coronary Artery Disease. NCT00176358
- Cardiac Rehabilitation for the Treatment of Refractory Angina NCT00411359
- Anti-Arrhythmic Effects of Exercise After an Implantable Cardioverter Defibrillator (ICD). NCT00522340
- Effect of Strict Glycemic Control on Improvement of Exercise Capacities (VO_2 Peak, Peak Workload) After Cardiac Rehabilitation in Patients With Type 2 Diabetes Mellitus With Coronary Artery Disease. NCT00354237
- Maintaining Exercise After Cardiac Rehabilitation. NCT00230724

Appendix A. Cardiac Rehabilitation/ Secondary Prevention Performance Measurement Set A [29]

Performance Measure A-1: Cardiac rehabilitation patient referral from an inpatient setting

All patients hospitalized with a primary diagnosis of an acute myocardial infarction (MI) or chronic stable angina (CSA), or who during hospitalization have undergone coronary artery bypass graft (CABG) surgery, a percutaneous coronary intervention (PCI), cardiac valve surgery, or cardiac transplantation are to be referred to an early outpatient cardiac rehabilitation/secondary prevention (CR) program.

Performance Measure A-2: Cardiac rehabilitation patient referral from an outpatient setting

All patients evaluated in an outpatient setting who within the past 12 months have experienced an acute myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, a percutaneous coronary intervention (PCI), cardiac valve surgery, or cardiac transplantation, or who have chronic stable angina (CSA) and have not already participated in an early outpatient cardiac rehabilitation/secondary prevention (CR) program for the qualifying event/diagnosis are to be referred to such a program.

Appendix B. Cardiac Rehabilitation/ Secondary Prevention Performance Measurement Set B [29]

Performance Measure B-1: Structure-based measurement set

The cardiac rehabilitation/secondary prevention (CR) program has policies in place to demonstrate that:

1 A physician-director is responsible for the oversight of CR program policies and procedures and ensures that policies and procedures are consistent with evidence-based guidelines, safety standards, and regulatory standards [38]. This includes appropriate policies and procedures for the provision of alternative CR program services, such as home-based CR.

2 An emergency response team is immediately available to respond to medical emergencies [38].

A In a hospital setting, physician supervision is presumed to be met when services are performed on hospital premises [12].

B In the setting of a free-standing outpatient CR program (owned/operated by a hospital, but not located on the main campus), a physician-directed emergency response team must be present and immediately available to respond to emergencies.

C In the setting of a physician-directed clinic or practice, a physician-directed emergency response team must be present and immediately available to respond to emergencies.

3 All professional staff have successfully completed the National Cognitive and Skills examination in accordance with the AHA curriculum for basic life support (BLS) with at least one staff member present who has completed the

National Cognitive and Skills examination in accordance with the AHA curriculum for advanced cardiac life support (ACLS) and has met state and hospital or facility medicolegal requirements for defibrillation and other related practices [38,100,101].
4 Functional emergency resuscitation equipment and supplies for handling cardiovascular emergencies are immediately available in the exercise area [38].

Performance Measure B-2: Assessment of risk for adverse cardiovascular events

The cardiac rehabilitation/secondary prevention (CR) program has the following processes in place:

1 Documentation, at program entry, that each patient undergoes an assessment of clinical status (e.g., symptoms, medical history) in order to identify high-risk conditions for adverse cardiovascular events.
2 A policy to provide recurrent assessments for each patient during the time of participation in the CR program in order to identify any changes in clinical status that increase the patient's risk of adverse cardiovascular events. If such findings are noted, the CR staff contacts the program's physician director and/or the patient's primary healthcare provider according to thresholds for communication included in the policies developed for Performance Measure B-3j.

Performance Measure B-3: Individualized assessment and evaluation of modifiable cardiovascular risk factors, development of individualized interventions, and communication with other healthcare providers

This performance measure includes 10 individual sub-measures for the evaluation of modifiable cardiovascular risk factors, development of individualized interventions, and communication with other healthcare providers concerning these risk factors and interventions.

The rationale for including both recognition *and* intervention for satisfactory fulfillment of these measures is predicated upon the belief that high-quality cardiovascular care requires both the identification and treatment of known cardiovascular risk factors.

An important component of this performance measure is the expectation that the cardiac rehabilitation/secondary prevention (CR) staff communicates with appropriate primary care providers and treating physicians in order to help coordinate risk factor management and to promote life-long adherence to lifestyle and pharmacological therapies. (See Performance Measure B-3j for more specific coverage of communication with the patient's primary healthcare provider.)

Performance Measure B-3a: Individualized assessment of tobacco use

For each eligible patient enrolled in the CR program, there is documentation that the following criteria have been met:

1 An assessment is made of current and past tobacco use.
2 If current tobacco use is identified, an intervention plan is recommended to the patient and communicated to the primary care provider and/or cardiologist. This plan may include individual education, counseling, and/or referral to a tobacco cessation program.
3 Prior to completion of the CR program, the patient's tobacco use status and tobacco avoidance treatment plan are reassessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3b: Individualized assessment of blood pressure (BP) control

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 An assessment is made of BP control, with target goals defined by the AHA/ACC secondary prevention guidelines.
2 For patients with a diagnosis of hypertension, an intervention plan is developed. This should include education about target BP goals, medication compliance, lifestyle modification for optimal dietary and physical activity habits, and weight control.
3 During the CR program, BP control is reassessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3c: Individualized assessment of optimal lipid control

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 An assessment of blood lipid control and use of lipid-lowering medications, with target goals defined by the AHA/ACC secondary prevention guidelines.
2 For patients with a diagnosis of hyperlipidemia, an intervention plan has been recommended to the patient. This should include education about target lipid goals, importance of medication compliance, lifestyle modification for optimal dietary and regular physical activity habits, and weight control.
3 Prior to completion of the CR program, lipid control and the lipid management plan, including lifestyle modification, are reassessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3d: Individualized assessment of physical activity habits

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 An assessment of current physical activity habits.
2 If physical activity habits at time of program entry do not meet suggested guidelines as defined by the AHA/ACC secondary prevention guidelines, then recommendations to improve physical activity habits are given to the patient.
3 Prior to completion of the CR program, physical activity habits and the physical activity intervention plan are reassessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3e: Individualized assessment of weight management

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 An assessment of body weight/composition, including the measurement of either body mass index (BMI) or waist circumference with targets as defined by the AHA/ACC secondary prevention guidelines [37].
2 If the body weight/composition measure(s) is (are) above recommended goal(s), then an intervention plan is recommended to the patient. This should include education about target goals and lifestyle modification including a healthy diet, behavior change, and regular physical activity and/or referral to a weight management program.
3 Prior to completion of the CR program, body weight/composition and the intervention plan are reassessed and communicated to the patient as well as the primary care provider and/or cardiologist.

Performance Measure B-3f: Individualized assessment of the diagnosis of diabetes mellitus (DM) or impaired fasting glucose (IFG)

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 Assessment of the diagnosis of IFG and DM, with definitions as described in the most recent American Diabetes Association Standards of Medical Care in Diabetes Position Statement [102].
2 If the patient has a diagnosis of IFG or DM, then an intervention plan is recommended to the patient for glycemic monitoring during exercise, for glycemic goals, and for recommendations concerning medical nutrition therapy and/or skill training sessions (if not previously attended).
3 Prior to completion of the CR program, DM/IFG status, and the DM/IFG intervention plan are reassessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3g: Individualized assessment of the presence or absence of depression

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 Assessment of the presence or absence of depression, using a valid and reliable screening tool.
2 If clinical depression is suspected as a result of screening, this has been discussed with the patient.
3 If clinical depression is suspected as a result of screening, the primary care provider and/or mental healthcare provider have been notified.

Performance Measure B-3h: Individualized assessment of exercise capacity

For each eligible patient enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criteria have been met:

1 Assessment of maximal or submaximal exercise capacity, using at least one of several possible assessment methods that has standard end points as defined by groups such as the American College of Sports Medicine and ACC/AHA practice guidelines and scientific statements [49,103].
2 An individualized exercise prescription, based on the assessment of exercise capacity, is recommended to the patient and communicated to the primary care provider and/or cardiologist.
3 Prior to completion of the CR program, change in exercise capacity is re-assessed and communicated to the patient as well as to the primary care provider and/or cardiologist.

Performance Measure B-3i: Individualized adherence to preventive medications

For each eligible patient with coronary artery disease enrolled in the cardiac rehabilitation/secondary prevention (CR) program, there is documentation that the following criterion has been met:

The patient has received individual or group education concerning the importance of adherence to preventive medications that are described in the AHA/ACC secondary prevention guidelines. (Note: Patients should be encouraged to discuss questions or concerns about prescribed preventive medications with their healthcare providers.)

Performance Measure B-3j: Communication with healthcare providers

There is a policy in place to ensure communication with healthcare providers, including individual patient status related to each modifiable risk factor at entrance to and completion of the cardiac rehabilitation/secondary prevention (CR) program, as well as when thresholds are met for more frequent or urgent communication concerning suboptimal risk factor control.

Performance Measure B-4: Monitor response to therapy and document program effectiveness

For each cardiac rehabilitation/secondary prevention (CR) program in a healthcare system, a written policy is in place to:

1 Document the percentage of patients for whom the CR program has received a formal referral request who actually enroll in the program.
2 Document for each patient a standardized plan to assess completion of the prescribed course of CR as defined on entrance to the program.
3 Document for each patient a standardized plan to assess outcome measurements at the initiation and again at the completion of CR, including at least one outcome measure for the core program components as outlined in the Cardiac Rehabilitation/Secondary Prevention Performance Measure Set B, Performance Measure 3.
4 Describe the program's methodology to document program effectiveness and initiate quality improvement strategies.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: The Impact of Prevention on Reducing the Burden of Cardiovascular Disease, http://circ.ahajournals.org/cgi/content/full/118/5/576 (an advocacy paper with ADA).

5 Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease

Sidney C. Smith, Jr.

Organization and evidence
Changes since publication of the 2006 Guidelines for Secondary Prevention
Comprehensive risk reduction for patients with coronary and other vascular disease
Smoking
Goal: Complete cessation, no exposure to environmental tobacco smoke
Blood pressure control
Goal: Less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease
Lipid management
Goal: LDL-C substantially less than 100 mg per dL
Physical activity
Goal: 30 minutes 5 days per week; optimal daily
Weight management
Goal: BMI: 18.5 to 24.9 kg/m^2
Diabetes management
Goal: HbA1c less than 7%
Antiplatelet agents/anticoagulants: aspirin
Antiplatelet agents/anticoagulants: clopidogrel
Antiplatelet agents/anticoagulants: warfarin
Renin–angiotensin–aldosterone system blockers: ACE inhibitors
Renin–angiotensin–aldosterone system blockers: angiotensin receptor blockers
Renin–angiotensin–aldosterone system blockers: aldosterone blockade
Beta-blockers
Influenza vaccination
Comparison with other guidelines
Ongoing research efforts and future directions

The AHA Guidelines and Scientific Statements Handbook
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Organization and evidence

Since the publication of the AHA/ACC Secondary Prevention guidelines in 2001 [1], compelling evidence has continued to evolve supporting the efficacy of intensive secondary prevention therapies to prevent future cardiovascular events in patients with established atherosclerotic vascular disease. This growing body of evidence confirms that comprehensive implementation of these therapies improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life for these patients. Evidence from many recent clinical trials and revised practice guidelines provided the impetus for this update of the 2001 Secondary Prevention Guidelines. Members of the writing group from AHA and ACC carefully reviewed the new evidence and presented the recommendations as they appear herein in using the current Classification of Recommendations and Level of Evidence as expressed in the ACC/AHA format.

Changes since publication of the 2006 Guidelines for Secondary Prevention

Recommendations put forth by the ATP III Update and JNC 7 are incorporated into these guideline recommendations. Findings from additional lipid reduction trials in more than 50,000 patients have resulted in optional lipid lowering targets for LDL-C of <70 mg/dL with a Class I recommendation that all patients with atherosclerotic vascular disease should have LDL-C <100 mg/dL. The JNC 7 recommendations for treatment of hypertension have

been incorporated into these guidelines. Specific recommendations for clopidogrel in patients with acute coronary syndromes and for those receiving bare metal and drug eluting stents have been incorporated into these guidelines. The results of three major trials involving ACE inibitors form the basis for recommendations about the use of these therapies among patients with atherosclerotic disease and normal left ventricular function. New recommendations for the use of aldosterone blockade therapy among patients with systolic heart failure and revised recommendations for beta blockade therapy are presented. For the first time a recommendation regarding influenza vaccine is presented with a Class I recommendation for its use in all patients with established atherosclerotic cardiovascular disease. The recommendations for physical activity have been upgrade to comply with recent NIH guidelines. The following guideline recommendations are those put forth in the AHA/ACC 2006 Secondary Prevention Update [2] as adapted and published in the 2007 PCI Focused Update [3].

We have presented this information both in text and table format (Table 5.1).

Comprehensive risk reduction for patients with coronary and other vascular disease

Smoking

Goal: Complete cessation, no exposure to environmental tobacco smoke

1 Status of tobacco use should be asked about at every visit. *I (B)*

2 Every tobacco user and family members who smoke should be advised to quit at every visit. *I (B)*

3 The tobacco user's willingness to quit should be assessed. *I (B)*

4 The tobacco user should be assisted by counseling and developing a plan for quitting. *I (B)*

5 Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and pharmacological treatment) should be arranged. *I (B)*

6 Exposure to environmental tobacco smoke at work and home should be avoided. *I (B)*

Blood pressure control

Goal: Less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease

1 For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is recommended to initiate or maintain lifestyle modification – weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. *I (B)*

2 For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure.* *I (A)*

Lipid management

Goal: LDL-C substantially less than 100 mg per dL

(If triglycerides are greater than or equal to 200 mg per dL, non-HDL-C should be less than 130 mg per dL†.)

1 Starting dietary therapy is recommended. Reduce intake of saturated fats (to less than 7% of total calories), trans fatty acids, and cholesterol (to less than 200 mg per day). *I (B)*

2 Adding plant stanol/sterols (2 g per day) and/or viscous fiber (greater than 10 g per day) is reasonable to further lower LDL-C. *IIa (A)*

3 Promotion of daily physical activity and weight management is recommended. *I (B)*

4 It may be reasonable to encourage increased consumption of omega-3 fatty acids in the form of

* For compelling indications for individual drug classes in specific vascular diseases, see the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

† Non-HDL-C indicates total cholesterol minus HDL-C.

fish‡ or in capsules (1 g per day) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction. *IIb (B)*

5 A fasting lipid profile should be assessed in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiation of lipid-lowering medication is indicated as recommended below before discharge according to the following schedule:

- LDL-C should be less than 100 mg per dL. *I (A)*
- Further reduction of LDL-C to less than 70 mg per dL is reasonable. *IIa (A)*
- If baseline LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy§ should be initiated. *I (A)*
- If on-treatment LDL-C is greater than or equal to 100 mg per dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination¶) is recommended. *I (A)*
- If baseline LDL-C is 70 to 100 mg per dL, it is reasonable to treat to LDL-C less than 70 mg per dL. *IIa (B)*
- If triglycerides are greater than or equal to 150 mg per dL or HDL-C is less than 40 mg per dL, weight management, physical activity, and smoking cessation should be emphasized. *I (B)*
- If triglycerides are 200 to 499 mg per dL††, non-HDL-C target should be less than 130 mg per dL. *I (B)*
- If triglycerides are 200 to 499 mg per dL††, further reduction of non-HDL-C to less than 100 mg per dL is reasonable. *IIa (B)*

6 Therapeutic options to reduce non-HDL-C include:

- More intense LDL-C-lowering therapy is indicated. *I (B)*
- Niacin (after LDL-C-lowering therapy) can be beneficial. *IIa (B)*
- Fibrate therapy‡‡ (after LDL-C-lowering therapy) can be beneficial. *IIa (B)*

7 If triglycerides are greater than or equal to 500 mg per dL,††§§ therapeutic options indicated and useful to prevent pancreatitis are fibrate§‡‡ or niacin§ before LDL-lowering therapy, and treat LDL-C to goal after triglyceride-lowering therapy. Achieving a non-HDL-C of less than 130 mg per dL is recommended. *I (C)*

Physical activity

Goal: 30 minutes 5 days per week; optimal daily

1 Advising medically supervised programs (cardiac rehabilitation) for high-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure) is recommended. *I (B)*

2 For all patients, it is recommended that risk be assessed with a physical activity history and/or an exercise test to guide prescription. *I (B)*

3 For all patients, encouraging 30 to 60 minutes of moderate-intensity aerobic activity is recommended, such as brisk walking on most – preferably all – days of the week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work). *I (B)*

4 Encouraging resistance training 2 days per week may be reasonable. *IIb (C)*

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‡ Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§ When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C less than 70 mg per dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C less than 70 mg per dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of greater than 50% in LDL-C levels by either statins or LDL-C-lowering drug combinations. Dietary supplement niacin must not be used as a substitute for prescription niacin.

¶ Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin.

†† The use of resin is relatively contraindicated when triglycerides are greater than 200 mg per dL.

‡‡ The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination.

§§ Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are greater than 200 mg/dL. _Some recommend avoiding regular use of ibuprofen, which may limit the cardioprotective effects of aspirin. Use of cyclooxygenase-2 inhibitors may be associated with an increased incidence of cardiovascular events.

Weight management

Goal: BMI: 18.5 to 24.9 kg/m^2

Waist circumference: men less than 40 inches (102 cm), women less than 35 inches (89 cm).

1 It is useful to assess BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2. *I (B)*

2 The initial goal of weight-loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. *I (B)*

3 If waist circumference (measured horizontally at the iliac crest) is 35 inches (89 cm) or greater in women and 40 inches (102 cm) or greater in men, it is useful to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. *I (B)*

Diabetes management

Goal: HbA1c less than 7%

1 It is recommended to initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c. *I (B)*

2 Beginning vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management as recommended above) is beneficial. *I (B)*

3 Coordination of diabetic care with the patient's primary care physician or endocrinologist is beneficial. *I (C)*

Antiplatelet agents/anticoagulants: aspirin

1 For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 162 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 75 mg to 162 mg daily. *I (B)*

2 In patients for whom the physician is concerned about risk of bleeding, lower-dose 75 mg to 162 mg of aspirin is reasonable during the initial period after stent implantation. *IIa (C)*

Antiplatelet agents/anticoagulants: clopidogrel

1 For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for *at least 12 months* if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and *ideally up to 12 months* (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). *I (B)*

2 For all post-PCI non-stented STEMI patients, treatment with clopidogrel should continue for at least 14 days. *I (B)*

3 Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy. *IIa (C)*

Antiplatelet agents/anticoagulants: warfarin

1 Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus). *I (A)*

2 Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. *I (B)*

3 In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75 mg dose of clopidogrel. *(1 C)*

Renin–angiotensin–aldosterone system blockers: ACE inhibitors

1 ACE inhibitors should be started and continued indefinitely in all patients with LVEF less than or equal to 40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. *I (A)*

2 ACE inhibitors should be started and continued indefinitely in patients who are not at lower risk, defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated. *I (B)*

3 Among lower risk patients (i.e., those with normal LVEF in whom cardiovascular risk factors are

Table 5.1 2007 PCI Recommendations

2007 PCI Recommendations	2007 COR and LOE
Smoking	
Goal: Complete cessation, no exposure to environmental tobacco smoke	
1. Status of tobacco use should be asked about at every visit.	I (B)
2. Every tobacco user and family members who smoke should be advised to quit at every visit.	I (B)
3. The tobacco user's willingness to quit should be assessed.	I (B)
4. The tobacco user should be assisted by counseling and developing a plan for quitting.	I (B)
5. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and pharmacological treatment) should be arranged.	I (B)
6. Exposure to environmental tobacco smoke at work and home should be avoided.	I (B)
Blood pressure control	
Goal: Less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease	
1. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is recommended to initiate or maintain lifestyle modification – weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.	I (B)
2. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure.	I (A)
Lipid management	
Goal: LDL-C substantially less than 100 mg per dL	
(If triglycerides are greater than or equal to 200 mg per dL, non-HDL-C should be less than 130 mg per dL[†].)	
1. Starting dietary therapy is recommended. Reduce intake of saturated fats (to less than 7% of total calories), trans fatty acids, and cholesterol (to less than 200 mg per day).	I (B)
2. Adding plant stanol/sterols (2 g per day) and/or viscous fiber (greater than 10 g per day) is reasonable to further lower LDL-C.	IIa (A)
3. Promotion of daily physical activity and weight management is recommended.	I (B)
4. It may be reasonable to encourage increased consumption of omega-3 fatty acids in the form of fish[‡] or in capsules (1 g per day) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.	IIb (B)
5. A fasting lipid profile should be assessed in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiation of lipid- lowering medication is indicated as recommended below before discharge according to the following schedule:	I (A)
• LDL-C should be less than 100 mg per dL.	I (A)
• Further reduction of LDL-C to less than 70 mg per dL is reasonable.	IIa (A)
• If baseline LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy[§] should be initiated.	I (A)
• If on-treatment LDL-C is greater than or equal to 100 mg per dL, intensifying LDL-lowering drug therapy (may require LDL-lowering drug combination[¶]) is recommended.	I (A)
• If baseline LDL-C is 70 to 100 mg per dL, it is reasonable to treat to LDL-C less than 70 mg per dL.	IIa (B)
If triglycerides are greater than or equal to 150 mg per dL or HDL-C is less than 40 mg per dL, weight management, physical activity, and weight management, physical activity, and smoking cessation should be emphasized.	I (B)

Table 5.1 *Continued*

2007 PCI Recommendations	2007 COR and LOE
• If triglycerides are 200 to 499 mg per dL[††], non-HDL-C target should be less than 130 mg per dL.	I (B)
• If triglycerides are 200 to 499 mg per dL[††], further reduction of non-HDL-C to less than 100 mg per dL is reasonable.	IIa (B)
6. Therapeutic options to reduce non-HDL-C include:	
• More intense LDL-C-lowering therapy is indicated.	I (B)
• Niacin[‖] (after LDL-C-lowering therapy) can be beneficial.	IIa (B)
• Fibrate therapy[‡‡] (after LDL-C-lowering therapy) can be beneficial.	IIa (B)
7. If triglycerides are greater than or equal to 500 mg per dL,[††§§] therapeutic options indicated and useful to prevent pancreatitis are fibrate[§‡‡] or niacin[§‖] before LDL-lowering therapy, and treating LDL-C to goal after triglyceride-lowering therapy. Achieving a non-HDL-C of less than 130 mg per dL is recommended.	I (C)
Physical activity	
Goal: 30 minutes days per week; optimal daily	
1. Advising medically supervised programs (cardiac rehabilitation) for high-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure) is recommended.	I (B)
2. For all patients, it is recommended that risk be assessed with a physical activity history and/or an exercise test to guide prescription.	I (B)
3. For all patients, encouraging 30 to 60 minutes of moderate-intensity aerobic activity is recommended, such as brisk walking on most – preferably all – days of the week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work).	I (B)
4. Encouraging resistance training 2 days per week may be reasonable.	IIb (C)
Weight management	
Goal: BMI: 18.5 to 24.9 kg/m^2	
Waist circumference: men less than 40 inches (102 cm) women less than 35 inches (89 cm)	
1. It is useful to assess BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2.	I (B)
2. The initial goal of weight-loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment.	I (B)
3. If waist circumference (measured horizontally at the iliac crest) is 35 inches (89 cm) or greater in women and 40 inches (102 cm) or greater in men, it is useful to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated.	I (B)
Diabetes management	
Goal: HbA_{1c} less than 7%	
1. It is recommended to initiate lifestyle changes and pharmacotherapy to achieve near-normal HbA_{1c}.	I (B)
2. Beginning vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management as recommended above) is beneficial.	I (B)
3. Coordination of diabetic care with the patient's primary care physician or endocrinologist is beneficial.	I (C)
Antiplatelet agents/anticoagulants: aspirin	
1. For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 162 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 75 mg to 162 mg daily.	**I (B)**

Table 5.1 *Continued*

2007 PCI Recommendations	2007 COR and LOE
2. In patients for whom the physician is concerned about risk of bleeding, lower-dose 75 mg to 162 mg of aspirin is reasonable during the initial period after stent implantation.	**IIa (C)**
Antiplatelet agents/anticoagulants: clopidogrel	
1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for *at least 12 months* if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for minimum of month and *ideally up to 12 months* (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).	**I (B)**
2. For all post-PCI non-stented STEMI patients, treatment with clopidogrel should continue for at least 14 days.	**I (B)**
3. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.	**IIa (C)**
Antiplatelet agents/anticoagulants: warfarin	
1. Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).	I (A)
2. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.	I (B)
3. In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel.	**I (C)**
Renin–angiotensin–aldosterone system blockers: ACE inhibitors	
1. ACE inhibitors should be started and continued indefinitely in all patients with LVEF less than or equal to 40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated.	I (A)
2. ACE inhibitors should be started and continued indefinitely in patients who are not lower risk (lower risk defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) unless contraindicated.	I (B)
3. Among lower risk patients (i.e., those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) use of ACE inhibitors is reasonable.	IIa (B)
Renin–angiotensin–aldosterone system blockers: angiotensin receptor blockers	
1. Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF less than or equal to 40%.	I (A)
2. Angiotensin receptor blockers are useful in other patients who are ACE-inhibitor intolerant and have hypertension.	**I (B)**
3. Considering use in combination with ACE inhibitors in systolic dysfunction HF may be reasonable.	IIb (B)
Renin–angiotensin–aldosterone system blockers: aldosterone blockade	
1. Use of aldosterone blockade in post-MI patients without significant renal dysfunction[¶¶] or hyperkalemia[***] is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have an LVEF of less than or equal to 40% and have either diabetes or HF.	I (A)
Beta blockers	
1. It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated.	I (A)
2. It is reasonable to consider long-term therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated.	IIa (C)

Table 5.1 *Continued*

2007 PCI Recommendations	2007 COR and LOE
Influenza vaccination	
1. Patients with cardiovascular disease should have an annual influenza vaccination.	I (B)

Recommendations in bold type are those the writing committee felt deserved extra emphasis. The 2007 PCI recommendations are written in complete sentences, in accordance with ACC/AHA Guidelines methodology. "No content change" indicates the updated recommendation which now includes a LOE and COR and a verb consistent with that LOE and COR as outlined in the ACC/AHA LOE/COR table (see table in the front of this book).

† Non-HDL-C indicates total cholesterol minus HDL-C.

‡ Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§ When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C less than 70 mg per dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C less than 70 mg per dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of greater than 50% in LDL-C levels by either statins or LDL-C-lowering drug combinations.

‖ Dietary supplement niacin must not be used as a substitute for prescription niacin.

¶ Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin.

†† The use of resin is relatively contraindicated when triglycerides are greater than 200 mg per dL.

‡‡ The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination.

§§ Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are greater than 200 mg/dL.

¶¶ Creatinine should be less than 2.5 mg per dL in men and less than 2.0 mg per dL in women.

*** Potassium should be less than 5.0 mEq per L.

ACE indicates angiotensin-converting enzyme; BMI, body mass index; COR, class of recommendation; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; INR,

well controlled and revascularization has been performed) use of ACE inhibitors is reasonable. *IIa (B)*

Renin–angiotensin–aldosterone system blockers: angiotensin receptor blockers

1 Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF less than or equal to 40%. *I (A)*

2 Angiotensin receptor blockers are useful in other patients who are ACE-inhibitor intolerant and have hypertension. *I (B)*

3 Considering use in combination with ACE inhibitors in systolic dysfunction HF may be reasonable. *IIb (B)*

Renin–angiotensin–aldosterone system blockers: aldosterone blockade

Use of aldosterone blockade in post-MI patients without significant renal dysfunction¶¶ orhyperkalemia*** is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have an LVEF of less than or equal to 40%, and have either diabetes or HF. *I (A)*

Beta-blockers

1 It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated. *I (A)*

2 It is reasonable to consider long-term therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated. *IIa (C)*

¶¶ Creatinine should be less than 2.5 mg per dL in men and less than 2.0 mg per dL in women.

*** Potassium should be less than 5.0 mEq per L. ACE indicates angiotensin-converting enzyme; BMI, body mass index; COR, class of recommendation; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Influenza vaccination

Patients with cardiovascular disease should have an annual influenza vaccination. *I (B)*

Comparison with other guidelines

These guideline recommendations are consistent with those from NIH including JNC 7 [4] and the ATP III Update [5,6]. The ESC guidelines [7] for prevention have similar recommendations regarding the risk factors to be treated with minor differences of target levels i.e. optional LDL-C of 80 mg/dL and HgB A1C of 6.5%. The ESC guidelines recommend different waist circumference target levels and do not include recommendations for influenza vaccine; however, both organizations emphasize the importance of comprehensive risk factor reduction to improve cardiovascular outcomes for patients with cardiovascular disease.

Ongoing research efforts and future directions

It is anticipated that additional evidence will be forthcoming regarding the treatment of dyslipidemia among patients with established CVD. Specifically information regarding optimal target levels for LDL-C and potential benefits derived from treating low HDL-C and increased triglycerides should be forthcoming. In addition the results of the ACCORD Trial [8,9] evaluating comprehensive risk factor control among patients with diabetes, as well as new guideline statements from JNC [8] regarding treatment of hypertension and ATP IV with recommendations on the management of dyslipidemia, are expected to result in an update of these recommendations.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

6 Percutaneous Coronary Intervention

Sidney C. Smith, Jr.

Organization and evidence
Changes since publication of the 2005 guidelines for PCI
Guideline recommendations
Outcomes
Acute outcome: procedural complications
Institutional and operator competency
Quality assurance
Operator and institutional volume
Role of on-site cardiac surgical backup
Primary PCI for STEMI without on-site cardiac surgery
Elective PCI without on-site surgery
Indications
Patients with asymptomatic ischemia or Canadian Cardiovascular Society (CCS) class I or II angina
Patients with CCS class III angina
Patients with unstable angina (UA)/NSTEMI
Patients with STEMI
Percutaneous intervention in patients with prior coronary bypass surgery
Management of patients undergoing PCI
Evolutions of technologies
Antiplatelet and antithrombotic adjunctive therapies for PCI
Post-PCI management
Special considerations
Clinical restenosis: background and management
Chronic kidney disease
Comparison with other guidelines
Ongoing research efforts and future directions

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Organization and evidence

Coronary heart disease (CHD) is the leading cause of death in the United States, and coronary revascularization with percutaneous coronary intervention (PCI) is an important and frequently performed therapy for this condition. In 2005, a writing group composed of representatives from the American College of Cardiology (ACC), American Heart Association (AHA), and Society for Cardiovascular Angiography and Interventions (SCAI) compiled an update of the 2001 ACC/AHA guidelines for PCI. The update [1] features recommendations driven by advances in stent design, including the introduction of drug-eluting stents (DES), as well as evidence on the use of adjunctive therapy with glycoprotein (GP) IIb/IIIa receptor antagonists, bivalirudin, and thienopyridines. In addition, important recommendations are made regarding the indication for and timing of PCI for the treatment of patients with acute coronary syndromes and the need for regular ongoing institutional and operator quality assessment. Special sections were presented that discussed angiographic predictors of success/complications, women, the elderly, diabetes mellitus, and comparisons with coronary bypass surgery [1].

Changes since publication of the 2005 Guidelines for PCI

In 2007, a focused update on PCI2 was compiled by the ACC/AHA/SCAI writing group, which made recommendations based on a review of evidence from clinical trials presented after the 2005 PCI update. Many of these trials were also considered in the 2007 ACC/AHA focused update on

ST-elevation myocardial infarction (STEMI) [3] and the 2007 guidelines for unstable angina/non-STEMI (NSTEMI) [4], and recommendations based on these data are consistent for all three guidelines. A new section with recommendations for the management of patients with chronic kidney disease has been added here. The 2007 guidelines have also been updated to include recommendations from the 2006 AHA/ACC guidelines on secondary prevention for patients with coronary and other atherosclerotic vascular disease [5] (see Chapter 5). The important role of the interventional cardiologist in implementing and supporting the benefits of these therapies is emphasized. The following guidelines therefore consist of the 2005 PCI guideline update as modified by the 2007 PCI focused update. The outline used in both the 2005 guideline update and 2007 focused update has been maintained in this chapter. Classification of recommendations and level of evidence are expressed in the standard ACC/AHA format.

Guideline recommendations

Outcomes

Acute outcome: procedural complications

Class I

All patients who have signs or symptoms suggestive of MI (myocardial infarction) during or after PCI and those with complicated procedures should have CK-MB (creatine kinase – MB) and troponin I or T measured after the procedure. *(Level of Evidence: B)*

Class IIa

Routine measurement of cardiac biomarkers (CK-MB and/or troponin I or T) in all patients undergoing PCI is reasonable 8 to 12 hours after the procedure. *(Level of Evidence: C)*

Refer to Fig. 6.1.

Institutional and operator competency

Quality assurance

Class I

1 An institution that performs PCI should establish an ongoing mechanism for valid peer review of its quality and outcomes. Review should be conducted both at the level of the entire program and at the level of the individual practitioner. Quality-assessment reviews should take risk adjustment, statistical power, and national benchmark statistics into consideration. Quality-assessment reviews should include both tabulation of adverse event rates for comparison with benchmark values and case review of complicated procedures and some uncomplicated procedures. *(Level of Evidence: C)*

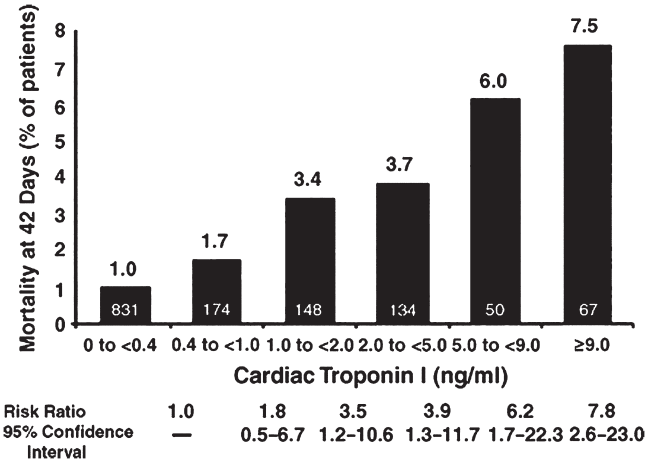

Fig. 6.1 Troponin I levels to predict the risk of mortality in acute coronary syndromes. Mortality rates are at 42 days (without adjustment for baseline characteristics) in patients with acute coronary syndrome. The numbers at the bottom of each bar are the numbers of patients with cardiac troponin I levels in each range, and the numbers above the bars are percentages. *P* less than 0.001 for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment. Reprinted with permission from Antman *et al.* [6]

2 An institution that performs PCI should participate in a recognized PCI data registry for the purpose of benchmarking its outcomes against current national norms. *(Level of Evidence: C)*

Operator and institutional volume

Class I

1 Elective PCI should be performed by operators with acceptable annual volume (at least 75 procedures) at high-volume centers (more than 400 procedures) with on-site cardiac surgery [7,8]. *(Level of Evidence: B)*

2 Elective PCI should be performed by operators and institutions whose historical and current risk-adjusted outcomes statistics are comparable to those reported in contemporary national data registries. *(Level of Evidence: C)*

3 Primary PCI for STEMI should be performed by experienced operators who perform more than 75 elective PCI procedures per year and, ideally, at least 11 PCI procedures for STEMI per year. Ideally, these procedures should be performed in institutions that perform more than 400 elective PCIs per year and more than 36 primary PCI procedures for STEMI per year. *(Level of Evidence B)*

Class IIa

1 It is reasonable that operators with acceptable volume (at least 75 PCI procedures per year) perform PCI at low-volume centers (200 to 400 PCI procedures per year) with on-site cardiac surgery [7,8]. *(Level of Evidence: B)*

2 It is reasonable that low-volume operators (fewer than 75 PCI procedures per year) perform PCI at high-volume centers (more than 400 PCI procedures per year) with on-site cardiac surgery [7,8]. Ideally, operators with an annual procedure volume less than 75 should only work at institutions with an activity level of more than 600 procedures per year. Operators who perform fewer than 75 procedures per year should develop a defined mentoring relationship with a highly experienced operator who has an annual procedural volume of at least 150 procedures per year. *(Level of Evidence: B)*

Class IIb

The benefit of primary PCI for STEMI patients eligible for fibrinolysis when performed by an operator who performs fewer than 75 procedures per year (or fewer than 11 PCIs for STEMI per year) is not well established. *(Level of Evidence: C)*

Class III

It is not recommended that elective PCI be performed by low-volume operators (fewer than 75 procedures per year) at low-volume centers (200 to 400) with or without on-site cardiac surgery. An institution with a volume of fewer than 200 procedures per year, unless in a region that is underserved because of geography, should carefully consider whether it should continue to offer this service. *(Level of Evidence: B)*

Refer to Table 6.1.

Role of on-site cardiac surgical backup

Class I

1 Elective PCI should be performed by operators with acceptable annual volume (at least 75 procedures per year) at high-volume centers (more than 400 procedures annually) that provide immediately available on-site emergency cardiac surgical services. *(Level of Evidence: B)*

2 Primary PCI for patients with STEMI should be performed in facilities with on-site cardiac surgery. *(Level of Evidence: B)*

Class III

Elective PCI should not be performed at institutions that do not provide on-site cardiac surgery. *(Level of Evidence: C)**

Primary PCI for STEMI without on-site cardiac surgery

Class IIb

Primary PCI for patients with STEMI might be considered in hospitals without on-site cardiac surgery, provided that appropriate planning for program

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* Several centers have reported satisfactory results based on careful case selection with well-defined arrangements for immediate transfer to a surgical program [12–22]. A small, but real fraction of patients undergoing elective PCI will experience a life-threatening complication that could be managed with the immediate on-site availability of cardiac surgical support but cannot be managed effectively by urgent transfer. Wennberg *et al.* [23] found higher mortality in the Medicare database for patients undergoing elective PCI in institutions without on-site cardiac surgery. This recommendation may be subject to revision as clinical data and experience increase.

Table 6.1 Patient selection for angioplasty and emergency aortocoronary bypass at hospitals without on-site cardiac surgery

Avoid intervention in hemodynamically stable patients with:

- Significant (greater than or equal to 60%) stenosis of an unprotected left main coronary artery upstream from an acute occlusion in the left coronary system that might be disrupted by the angioplasty catheter
- Extremely long or angulated infarct-related lesions with TIMI grade 3 flow
- Infarct-related lesions with TIMI grade 3 flow in stable patients with 3-vessel disease [9,10]
- Infarct-related lesions of small or secondary vessels
- Lesions in other than the infarct artery

Transfer for emergent aortocoronary bypass surgery patients with:

- High-grade residual left main or multivessel coronary disease and clinical or hemodynamic instability

– After angioplasty or occluded vessels

– Preferably with intra-aortic balloon pump support

Adapted with permission from Wharton *et al.* [11].

development has been accomplished, including appropriately experienced physician operators (more than 75 total PCIs and, ideally, at least 11 primary PCIs per year for STEMI), an experienced catheterization team on a 24 hours per day, 7 days per week call schedule, and a well-equipped catheterization laboratory with digital imaging equipment, a full array of interventional equipment, and intra-aortic balloon pump capability, and provided that there is a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with STEMI or MI with new or presumably new left bundle-branch block on ECG (electrocardiograph) and should be performed in a timely fashion (goal of balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals that perform a minimum of 36 primary PCI procedures per year. *(Level of Evidence: B)*

Class III

Primary PCI should not be performed in hospitals without on-site cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. *(Level of Evidence: C)*

Elective PCI without on-site surgery

Class III

Elective PCI should not be performed at institutions that do not provide on-site cardiac surgery. *(Level of Evidence: C)*†

Indications

Patients with asymptomatic ischemia or Canadian Cardiovascular Society (CCS) class I or II angina

Class IIa

1 PCI is reasonable in patients with asymptomatic ischemia or CCS class I or II angina and with 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI with a high likelihood of success and a low risk of morbidity and mortality. The vessels to be dilated must subtend a moderate to large area of

†Several centers have reported satisfactory results based on careful case selection with well-defined arrangements for immediate transfer to a surgical program [12–22]. A small, but real fraction of patients undergoing elective PCI will experience a life-threatening complication that could be managed with the immediate on-site availability of cardiac surgical support but cannot be managed effectively by urgent transfer. Wennberg *et al.* [23] found higher mortality in the Medicare database for patients undergoing elective PCI in institutions without on-site cardiac surgery. This recommendation may be subject to revision as clinical data and experience increase.

viable myocardium or be associated with a moderate to severe degree of ischemia on noninvasive testing. *(Level of Evidence: B)*

2 PCI is reasonable for patients with asymptomatic ischemia or CCS class I or II angina and recurrent stenosis after PCI with a large area of viable myocardium or high-risk criteria on noninvasive testing. *(Level of Evidence: C)*

3 Use of PCI is reasonable in patients with asymptomatic ischemia or CCS class I or II angina with significant left main CAD (coronary artery disease; greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG. *(Level of Evidence: B)*

Class IIb

1 The effectiveness of PCI for patients with asymptomatic ischemia or CCS class I or II angina who have 2- or 3-vessel disease with significant proximal LAD (left anterior descending coronary artery) CAD who are otherwise eligible for CABG (coronary artery bypass grafting) with 1 arterial conduit and who have treated diabetes or abnormal LV (left ventricular) function is not well established. *(Level of Evidence: B)*

2 PCI might be considered for patients with asymptomatic ischemia or CCS class I or II angina with nonproximal LAD CAD that subtends a moderate area of viable myocardium and demonstrates ischemia on noninvasive testing. *(Level of Evidence: C)*

Class III

PCI is not recommended in patients with asymptomatic ischemia or CCS class I or II angina who do not meet the criteria as listed under the class II recommendations or who have 1 or more of the following:

a. Only a small area of viable myocardium at risk *(Level of Evidence: C)*
b. No objective evidence of ischemia. *(Level of Evidence: C)*
c. Lesions that have a low likelihood of successful dilatation. *(Level of Evidence: C)*
d. Mild symptoms that are unlikely to be due to myocardial ischemia. *(Level of Evidence: C)*
e. Factors associated with increased risk of morbidity or mortality. *(Level of Evidence: C)*
f. Left main disease and eligibility for CABG. *(Level of Evidence: C)*
g. Insignificant disease (less than 50% coronary stenosis). *(Level of Evidence: C)*

Patients with CCS class III angina

Class IIa

1 It is reasonable that PCI be performed in patients with CCS class III angina and single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more significant lesions in 1 or more coronary arteries suitable for PCI with a high likelihood of success and low risk of morbidity or mortality. *(Level of Evidence: B)*

2 It is reasonable that PCI be performed in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery. *(Level of Evidence: C)*

3 Use of PCI is reasonable in patients with CCS class III angina with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG. *(Level of Evidence: B)*

Class IIb

1 PCI may be considered in patients with CCS class III angina with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success. *(Level of Evidence: B)*

2 PCI may be considered in patients with CCS class III angina and no evidence of ischemia on noninvasive testing or who are undergoing medical therapy and have 2- or 3-vessel CAD with significant proximal LAD CAD and treated diabetes or abnormal LV function. *(Level of Evidence: B)*

Class III

PCI is not recommended for patients with CCS class III angina with single-vessel or multivessel CAD, no evidence of myocardial injury or ischemia on

Table 6.2 Causes of UA/NSTEMI*

Thrombus or thromboembolism, usually arising on disrupted or eroded plaque
• Occlusive thrombus, usually with collateral vessels†
• Subtotally occlusive thrombus on pre-existing plaque
• Distal microvascular thromboembolism from plaque-associated thrombus
Thromboembolism from plaque erosion
• Non-plaque-associated coronary thromboembolism
Dynamic obstruction (coronary spasm‡ or vasoconstriction) of epicardial and/or microvascular vessels
Progressive mechanical obstruction to coronary flow
Coronary arterial inflammation
Secondary UA
Coronary artery dissection§

*These causes are not mutually exclusive; some patients have two or more causes.

†From DeWood *et al.* [24].

‡May occur on top of an atherosclerotic plaque, producing missed-etiology angina or UA/NSTEMI.

§Rare.

Table modified with permission from Braunwald [25].

objective testing, and no trial of medical therapy, or who have 1 of the following:

a. Only a small area of myocardium at risk. *(Level of Evidence: C)*
b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. *(Level of Evidence: C)*
c. A high risk of procedure-related morbidity or mortality. *(Level of Evidence: C)*
d. Insignificant disease (less than 50% coronary stenosis). *(Level of Evidence: C)*
e. Significant left main CAD and candidacy for CABG. *(Level of Evidence: C)*

Patients with unstable angina (UA)/NSTEMI

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 have characteristics that make them candidates for invasive therapy (see Table 6.2 and Section 3.3 of the ACC/AHA 2007 UA/NSTEMI guidelines) [4]. *(Level of Evidence: A)*

2 PCI (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*

3 PCI (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. *(Level of Evidence: A)*

4 An intravenous platelet GP IIb/IIIa inhibitor is useful in UA/NSTEMI patients undergoing PCI. *(Level of Evidence: A)* See Section 3.2.3 of the 2007 ACC/AHA 2007 UA/NSTEMI guidelines and Table 6.2 [4].

5 An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). *(Level of Evidence: B)*

Class IIa

1 PCI is reasonable for focal saphenous vein graft lesions or multiple stenoses in UA/NSTEMI patients who are undergoing medical therapy and who are

‡For example, severe hepatic, pulmonary, or renal failure, or active/inoperable cancer. Clinical judgment is required in such cases.

Table 6.3 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 LV function (LVEF less than 0.40)
Conservative	Low-risk score (e.g., TIMI, GRACE)
	Patient or physician preference in absence of high-risk features

Reprinted from the ACC/AHA 2007 UA/NSTEMI guidelines [4].

GRACE indicates Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; TIMI, Thrombolysis In Myocardial Infarction; TnI, troponin I; and TnT, troponin T.

poor candidates for reoperative surgery. *(Level of Evidence: C)*

2 PCI (or CABG) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. *(Level of Evidence: B)*

3 PCI (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal LAD CAD. *(Level of Evidence: 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 emergency intervention at angiography for hemodynamic instability. *(Level of Evidence: 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 1 or more lesions to be dilated with a reduced likelihood of success. *(Level of Evidence: B)*

2 PCI may be considered in patients with UA/NSTEMI who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal LAD CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy. *(Level of Evidence: B)*

3 In initially stabilized patients, an initially conservative (i.e., a selectively invasive) strategy may be considered as a treatment strategy for UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures§) who have an elevated risk for clinical events (see Table 6.3), including those who are troponin positive. *(Level of Evidence: B)*. The decision to implement an initial conservative (versus initial invasive) strategy‖ in these patients may be made by considering physician and patient preference. *(Level of Evidence: C)*

4 An invasive strategy may be reasonable in patients with chronic renal insufficiency. *(Level of Evidence: C)*

Refer to Figure 6.2.

§For example, severe hepatic, pulmonary, or renal failure, or active/inoperable cancer. Clinical judgment is required in such cases.

‖Diagnostic angiography with intent to perform revascularization.

Class III

1 PCI (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal LAD CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. *(Level of Evidence: 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. *(Level of Evidence: C)*

b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. *(Level of Evidence: C)*

c. A high risk of procedure-related morbidity or mortality. *(Level of Evidence: C)*

d. Insignificant disease (less than 50% coronary stenosis). *(Level of Evidence: C)*

e. Significant left main CAD and candidacy for CABG. *(Level of Evidence: B)*

3 A PCI strategy in stable patients (see Table 12 of the 2007 focused update on PCI, Class III recommendation No. 1, for details [2]) with persistently occluded infarct-related coronary arteries after STEMI/NSTEMI is not indicated. *(Level of Evidence: B)*

Patients with STEMI

General and specific considerations

Class I

General considerations If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new left bundle-branch block who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation goal within 90 minutes of presentation) by persons skilled in the procedure (individuals who perform more than 75 PCI procedures per year, ideally at least 11 PCIs per year for STEMI). The procedure should be supported by experienced personnel in an appropriate laboratory environment (one that performs more than 200 PCI procedures per year, of which at least 36 are primary PCI for STEMI, and that has cardiac surgery capability). *(Level of Evidence: A)* Primary PCI should be performed as quickly as possible, with a goal of a medical contact-to-balloon or door-to-balloon time within 90 minutes. *(Level of Evidence: B)*

Specific considerations

2 Primary PCI should be performed for patients less than 75 years old with ST elevation or presumably new left bundle-branch block who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*

3 Primary PCI should be performed in patients with severe congestive heart failure and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. The medical contact-to-balloon or door-to-balloon time should be as short as possible (i.e., goal within 90 minutes). *(Level of Evidence: B)*

Class IIa

1 Primary PCI is reasonable for selected patients 75 years or older with ST elevation or left bundle-branch block or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

2 It is reasonable to perform primary PCI for patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:

a. Severe congestive heart failure *(Level of Evidence: C)*

b. Hemodynamic or electrical instability *(Level of Evidence: C)*

c. Evidence of persistent ischemia *(Level of Evidence: C)*

Class IIb

The benefit of primary PCI for STEMI patients eligible for fibrinolysis when performed by an operator who performs fewer than 75 PCI procedures per year (or fewer than 11 PCIs for STEMI per year) is not well established. *(Level of Evidence: C)*

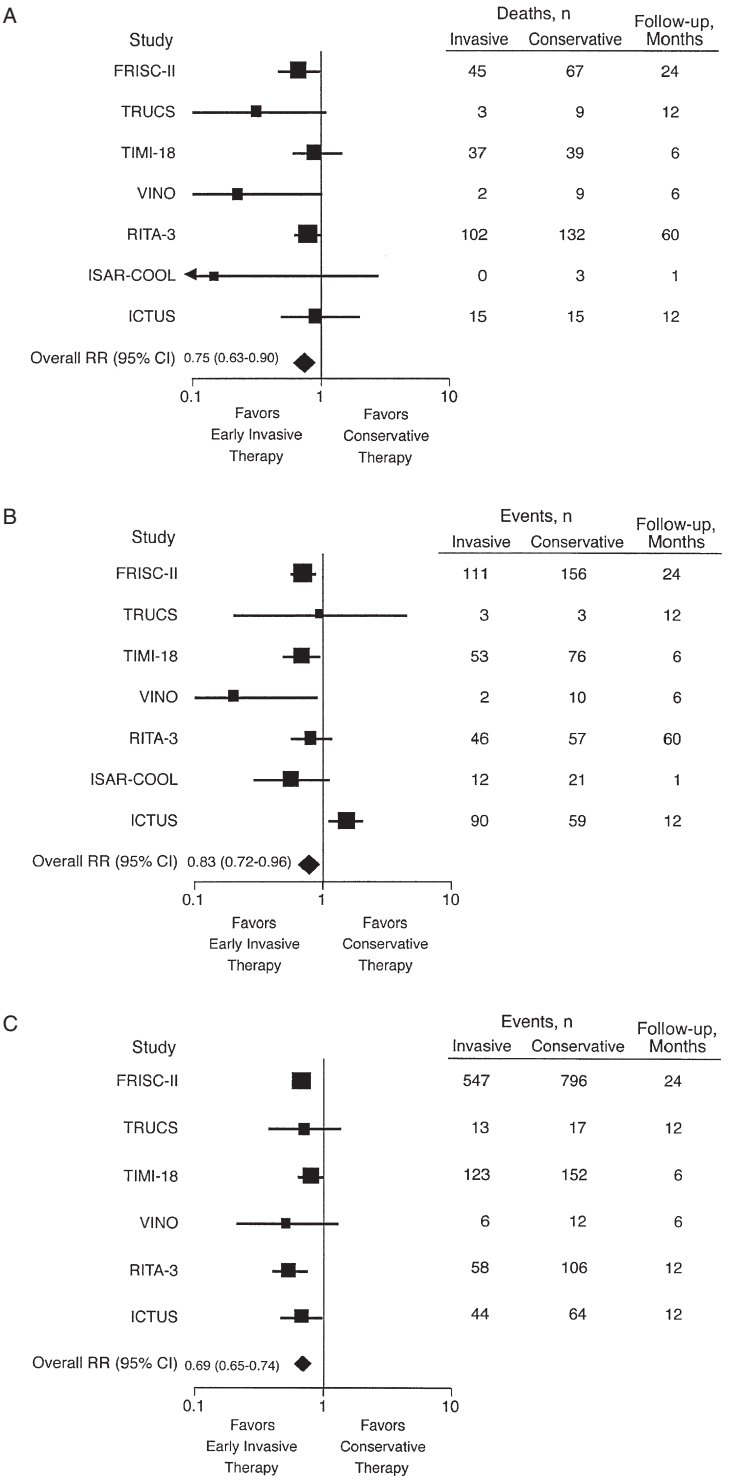

Fig. 6.2 Relative risk of outcomes with early invasive versus conservative therapy in UA/NSTEMI. (a) Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. (b) Relative risk of recurrent nonfatal MI for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. (c) Relative risk of recurrent UA resulting in rehospitalization for early invasive therapy compared with conservative therapy at a mean follow-up of 13 months. CI indicates confidence interval; FRISC-II, FRagmin and fast Revascularization during InStability in Coronary artery disease; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; ISAR-COOL, Intracoronary Stenting with Antithrombotic Regimen COOLing-off study; RITA-3, Third Randomized Intervention Treatment of Angina trial; RR, relative risk; TIMI-18, Thrombolysis In Myocardial Infarction-18; TRUCS, Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery; and VINO, Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: Open multicenter randomized trial. Reprinted from the Journal of the American College of Cardiology, vol. 48, Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials, pp. 1319–1325, Copyright 2006 by American College of Cardiology Foundation.

Class III

1 Elective PCI should not be performed in a non–infarct-related artery at the time of primary PCI of the infarct-related artery in patients without hemodynamic compromise. *(Level of Evidence: C)*
2 Primary PCI should not be performed in asymptomatic patients more than 12 hours after onset of STEMI if they are hemodynamically and electrically stable. *(Level of Evidence: C)*

PCI in fibrinolytic-ineligible patients

Class I

Primary PCI should be performed in fibrinolytic-ineligible patients who present with STEMI within 12 hours of symptom onset. *(Level of Evidence: C)*

Class IIa

It is reasonable to perform primary PCI for fibrinolytic-ineligible patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:

a. Severe congestive heart failure. *(Level of Evidence: C)*
b. Hemodynamic or electrical instability. *(Level of Evidence: C)*
c. Evidence of persistent ischemia. *(Level of Evidence: C)*

Facilitated PCI

Class IIb

Facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered as a reperfusion strategy when all of the following are present:

a. Patients are at high risk
b. PCI is not immediately available within 90 minutes, and
c. Bleeding risk is low (younger age, absence of poorly controlled hypertension, normal body weight). *(Level of Evidence: C)*

Class III

A planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI may be harmful. *(Level of Evidence: B)*

PCI after failed fibrinolysis (rescue PCI)

Class I

A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is recommended for patients who have received fibrinolytic therapy and have any of the following:

a. Cardiogenic shock in patients less than 75 years old who are suitable candidates for revascularization. *(Level of Evidence: B)*
b. Severe congestive heart failure and/or pulmonary edema (Killip class III). *(Level of Evidence: B)*
c. Hemodynamically compromising ventricular arrhythmias. *(Level of Evidence: C)*

Class IIa

1 A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is reasonable in patients 75 years of age or older who have received fibrinolytic therapy and are in cardiogenic shock, provided that they are suitable candidates for revascularization. *(Level of Evidence: B)*
2 It is reasonable to perform rescue PCI for patients with 1 or more of the following:
a. Hemodynamic or electrical instability. *(Level of Evidence: C)*
b. Persistent ischemic symptoms. *(Level of Evidence: C)*
3 A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation less than 50% resolved after 90 minutes following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and a moderate or large area of myocardium at risk (anterior MI, inferior MI with right ventricular involvement, or precordial ST-segment depression). *(Level of Evidence: B)*

Class IIb

A strategy of coronary angiography with intent to perform PCI in the absence of 1 or more of the above class I or IIa indications might be reasonable in moderate- and high-risk patients, but its benefits and risks are not well established. The benefits of rescue PCI are greater the earlier it is initiated after the onset of ischemic discomfort. *(Level of Evidence: C)*

Class III

A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is not recommended in patients who have received fibrinolytic therapy if further invasive management is contraindicated or the patient or designee does not wish further invasive care. *(Level of Evidence: C)*

PCI after successful fibrinolysis or for patients not undergoing primary reperfusion

Class I

1 In patients whose anatomy is suitable, PCI should be performed when there is objective evidence of recurrent MI. *(Level of Evidence: C)*

2 In patients whose anatomy is suitable, PCI should be performed for moderate or severe spontaneous or provocable myocardial ischemia during recovery from STEMI. *(Level of Evidence: B)*

3 In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to perform routine PCI in patients with LV ejection fraction less than or equal to 0.40, heart failure, or serious ventricular arrhythmias. *(Level of Evidence: C)*

2 It is reasonable to perform PCI when there is documented clinical heart failure during the acute episode, even though subsequent evaluation shows preserved LV function (LV ejection fraction greater than 0.40). *(Level of Evidence: C)*

Class IIb

PCI of a hemodynamically significant stenosis in a patent infarct artery greater than 24 hours after STEMI may be considered as part of an invasive strategy. *(Level of Evidence: B)*

Class III

PCI of a totally occluded infarct artery greater than 24 hours after STEMI is not recommended in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia. *(Level of Evidence: B)*

Ancillary therapy for patients undergoing PCI for STEMI

Class I

For patients undergoing PCI after having received an anticoagulant regimen, the following dosing recommendations should be adhered to:

a. For prior treatment with UFH (unfractionated heparin), administer additional boluses of UFH as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. *(Level of Evidence: C)* Bivalirudin may also be used in patients treated previously with UFH. *(Level of Evidence: C)*

b. For prior treatment with enoxaparin, if the last subcutaneous dose was administered at least 8 to 12 hours earlier, an intravenous dose of enoxaparin 0.3 mg per kilogram should be given; if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given. (*Level of Evidence: B*)

c. For prior treatment with fondaparinux, administer additional intravenous treatment with an anticoagulant possessing anti-IIa activity, taking into account whether GP IIb/IIIa receptor antagonists have been administered. *(Level of Evidence: C)*

Class III

Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered. *(Level of Evidence: C)*

PCI for cardiogenic shock

Class I

Primary PCI is recommended for patients less than 75 years old with ST elevation or left bundle-branch block who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*

Class IIa

Primary PCI is reasonable for selected patients 75 years or older with ST elevation or left bundle-branch block who develop shock within 36 hours of MI and

Table 6.4 Recommendations for Primary PCI in Acute Transmural MI Patients as an Alternative to Thrombolysis

Class I	Class IIa	Class III
As an alternative to thrombolytic therapy in patients with AMI and ST-segment elevation or new or presumed new left bundle-branch block who can undergo angioplasty of the infarct artery within12 h from the onset of ischemic symptoms or more than 12 h later if symptoms persist, if performed in a timely fashion* by individuals skilled in the procedure† and supported by experienced personnel in an appropriate laboratory environment.‡ *(Level of Evidence: A)* In patients who are within 36 h of an acute ST-elevation/Q-wave or new left bundle-branch block MI who develop cardiogenic shock and are less than 75 years of age, and revascularization can be performed within 18 h of the onset of shock by individuals skilled in the procedure† and supported by experienced personnel in an appropriate laboratory experiment.‡ *(Level of Evidence: A)*	As a reperfusion strategy in candidates who have a contraindication to thrombolytic therapy. *(Level of Evidence: C)*	Elective PCI of a non-infarct-related artery at the time of acute MI. *(Level of Evidence: C)* In patients with acute MI who: have received fibrinolytic therapy within 12 h and have no symptoms of myocardial ischemia; are eligible for thrombolytic therapy and are undergoing primary angioplasty by an inexperienced operator§; care beyond 12 h after onset of symptoms and have no evidence of myocardial ischemia. *(Level of Evidence: C)*

* Performance standard: balloon inflation within 90 ± 30 min of hospital admission.

† Individuals who perform ≥75 or more PCI procedures per year.

‡ Centers that perform more than 200 PCI procedures per year and have cardiac surgical capability.

§ Individual who performs fewer than <75 PCI procedures per year [27,28].

AMI indicates acute myocardial infarction; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

Refer to Table 6.4.

Percutaneous intervention in patients with prior coronary bypass surgery

Class I

1 When technically feasible, PCI should be performed in patients with early ischemia (usually within 30 days) after CABG. *(Level of Evidence: B)*

2 It is recommended that distal embolic protection devices be used when technically feasible in patients undergoing PCI to saphenous vein grafts. *(Level of Evidence: B)*

Class IIa

1 PCI is reasonable in patients with ischemia that occurs 1 to 3 years after CABG and who have preserved LV function with discrete lesions in graft conduits. *(Level of Evidence: B)*

2 PCI is reasonable in patients with disabling angina secondary to new disease in a native coronary circulation after CABG. (If angina is not typical, objective evidence of ischemia should be obtained.) *(Level of Evidence: B)*

3 PCI is reasonable in patients with diseased vein grafts more than 3 years after CABG. *(Level of Evidence: B)*

4 PCI is reasonable when technically feasible in patients with a patent left internal mammary artery graft who have clinically significant obstructions in other vessels. *(Level of Evidence: C)*

Class III

1 PCI is not recommended in patients with prior CABG for chronic total vein graft occlusions. *(Level of Evidence: B)*

2 PCI is not recommended in patients who have multiple target lesions with prior CABG and who have multivessel disease, failure of multiple SVGs (saphenous vein grafts), and impaired LV function unless repeat CABG poses excessive risk due to severe comorbid conditions. *(Level of Evidence: B)*

Intravascular ultrasound imaging (IVUS)

Class IIa

IVUS is reasonable for the following:

a. Assessment of the adequacy of deployment of coronary stents, including the extent of stent apposition and determination of the minimum luminal diameter within the stent. *(Level of Evidence: B)*

b. Determination of the mechanism of stent restenosis (inadequate expansion versus neointimal proliferation) and to enable selection of appropriate therapy (vascular brachytherapy versus repeat balloon expansion). *(Level of Evidence: B)*

c. Evaluation of coronary obstruction at a location difficult to image by angiography in a patient with a suspected flow-limiting stenosis. *(Level of Evidence: C)*

d. Assessment of a suboptimal angiographic result after PCI. *(Level of Evidence: C)*

e. Establishment of the presence and distribution of coronary calcium in patients for whom adjunctive rotational atherectomy is contemplated. *(Level of Evidence: C)*

f. Determination of plaque location and circumferential distribution for guidance of directional coronary atherectomy. *(Level of Evidence: B)*

Class IIb

IVUS may be considered for the following:

a. Determination of the extent of atherosclerosis in patients with characteristic anginal symptoms and a positive functional study with no focal stenoses or mild CAD on angiography. *(Level of Evidence: C)*

b. Preinterventional assessment of lesional characteristics and vessel dimensions as a means to select an optimal revascularization device. *(Level of Evidence: C)*

c. Diagnosis of coronary disease after cardiac transplantation. *(Level of Evidence: C)*

Class III

IVUS is not recommended when the angiographic diagnosis is clear and no interventional treatment is planned. *(Level of Evidence: C)*

Coronary artery pressure and flow: use of fractional flow reserve and coronary vasodilatory reserve

Class IIa

It is reasonable to use intracoronary physiologic measurements (Doppler ultrasound, fractional flow reserve) in the assessment of the effects of intermediate coronary stenoses (30% to 70% luminal narrowing) in patients with anginal symptoms. Coronary pressure or Doppler velocimetry may also be useful as an alternative to performing noninvasive functional testing (e.g., when the functional study is absent or ambiguous) to determine whether an intervention is warranted. *(Level of Evidence: B)*

Class IIb

1 Intracoronary physiologic measurements may be considered for the evaluation of the success of PCI in restoring flow reserve and to predict the risk of restenosis. *(Level of Evidence: C)*

2 Intracoronary physiologic measurements may be considered for the evaluation of patients with anginal symptoms without an apparent angiographic culprit lesion. *(Level of Evidence: C)*

Class III

Routine assessment with intracoronary physiologic measurements such as Doppler ultrasound or fractional flow reserve to assess the severity of angiographic disease in patients with a positive, unequivocal noninvasive functional study is not recommended. *(Level of Evidence: C)*

Management of patients undergoing PCI

Evolutions of technologies

Acute results

Class I

It is recommended that distal embolic protection devices be used when technically feasible in patients undergoing PCI to saphenous vein grafts. *(Level of Evidence: B)*

Antiplatelet and antithrombotic adjunctive therapies for PCI

Oral antiplatelet therapy

Class I

1 Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed. *(Level of Evidence: A)*

2 Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed. *(Level of Evidence: C)*

3 After PCI, in patients without allergy or increased risk of bleeding, aspirin 162 to 325 mg daily should be given for at least 1 month after BMS (bare-metal stent) implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily long-term aspirin use should be continued indefinitely at a dose of 75 to 162 mg. *(Level of Evidence: B)*

4 A loading dose of clopidogrel,¶ generally 600 mg, should be administered before or when PCI is performed. *(Level of Evidence: C)* In patients undergoing PCI within 12 to 24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered. *(Level of Evidence: C)*

5 For all post-PCI stented patients receiving a DES, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). *(Level of Evidence: B)*

Class IIa

1 If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial. *(Level of Evidence: B)*

2 For patients with an absolute contraindication to aspirin, it is reasonable to give a 300 to 600 mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI. *(Level of Evidence: C)*

3 In patients for whom the physician is concerned about risk of bleeding, a lower dose of 75 to 162 mg of aspirin is reasonable during the initial period after stent implantation. *(Level of Evidence: C)*

Class IIb

Continuation of clopidogrel therapy beyond 1 year may be considered in patients undergoing DES placement. *(Level of Evidence: C)*

GP IIb/IIIa inhibitors

Class I

In patients with UA/NSTEMI undergoing PCI without clopidogrel administration, a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) should be administered. *(Level of Evidence: A)*#

Class IIa

1 In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). *(Level of Evidence: B)*#

2 In patients with STEMI undergoing PCI, it is reasonable to administer abciximab as early as possible. *(Level of Evidence: B)*

3 In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). *(Level of Evidence: B)*

Class IIb

In patients with STEMI undergoing PCI, treatment with eptifibatide or tirofiban may be considered. *(Level of Evidence: C)*

Refer to Table 6.5.

¶Some uncertainty exists about the optimal loading dose of clopidogrel. 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 more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and safety of higher oral loading doses have not been rigorously established.

#It is acceptable to administer the GP IIb/IIIa inhibitor before performance of the diagnostic angiogram ("upstream treatment") or just before PCI ("in-lab treatment").

Table 6.5 Medications used for stabilized UA/NSTEMI 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 factor**	**Class/Level of Evidence**
HMG-CoA reductase inhibitors	LDL cholesterol greater than 70 mg per dL	Ia
Fibrates	HDL cholesterol less than 40 mg per dL	IIa/B
Niacin	HDL cholesterol less than 40 mg per dL	IIa/B
Niacin or fibrate	Triglycerides 200 mg per dL	IIa/B
Antidepressant	Treatment of depression	IIb/B
Treatment of hypertension	Blood pressure greater than 140/90 mm Hg or greater than 130/80 mm Hg if kidney disease or diabetes present	I/A
Treatment of diabetes	HbA_{1C} greater than 7%	I/B
Hormone therapy (initiation)†	Postmenopausal state	III/A
Hormone therapy (continuation)†	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, B6, B12	Antioxidant effect; homocysteine lowering	III/A

*Preferred to ticlopidine.

†For risk reduction of coronary artery disease.

ACEI indicates angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; COX-2, cyclooxygenase 2; EF, ejection fraction; HDL, high-density lipoprotein; HF, heart failure; HMG-CoA, hydroxymethyl glutaryl coenzyme A; INR, international normalized ratio; LDL, low-density lipoprotein; NSAID, nonsteroidal antiinflammatory drug; NSTEMI, non-ST-segment elevation myocardial infarction; and UA, unstable angina.

Antithrombotic therapy

UFH, low-molecular-weight heparin, and bivalirudin

Class I

1 UFH should be administered to patients undergoing PCI. *(Level of Evidence: C)*

2 For patients with heparin-induced thrombocytopenia, it is recommended that bivalirudin or argatroban be used to replace heparin. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to use bivalirudin as an alternative to UFH and GP IIb/IIIa antagonists in low-risk patients undergoing elective PCI. *(Level of Evidence: B)*

2 Low-molecular-weight heparin is a reasonable alternative to UFH in patients with UA/NSTEMI undergoing PCI. *(Level of Evidence: B)*

Class IIb

Low-molecular-weight heparin may be considered as an alternative to UFH in patients with STEMI undergoing PCI. *(Level of Evidence: B)*

Post-PCI management

Left main CAD

Class IIa

It is reasonable that patients undergoing PCI to unprotected left main coronary obstructions be followed up with coronary angiography between 2 and 6 months after PCI. *(Level of Evidence: C)*

Special considerations

Clinical restenosis: background and management

Management strategies for restenosis after PTCA

Class IIa

It is reasonable to consider that patients who develop restenosis after PTCA or PTCA with atheroablative devices are candidates for repeat coronary intervention with intracoronary stents if anatomic factors are appropriate. *(Level of Evidence: B)*

DES and BMS

Class I

1 A DES should be considered as an alternative to a BMS in those patients for whom clinical trials indicate a favorable effectiveness/safety profile. *(Level of Evidence: A)*

2 Before implanting a DES, the interventional cardiologist should discuss with the patient the need for and duration of DAT (dual-antiplatelet therapy) and confirm the patient's ability to comply with the recommended therapy for DES. *(Level of Evidence: B)*

3 In patients who are undergoing preparation for PCI and are likely to require invasive or surgical procedures for which DAT must be interrupted during the next 12 months, consideration should be given to implantation of a BMS or performance of balloon angioplasty with a provisional stent implantation instead of the routine use of a DES. *(Level of Evidence: C)*

Class IIa

In patients for whom the physician is concerned about risk of bleeding, a lower dose of 75 to 162 mg of aspirin is reasonable. *(Level of Evidence: C)*

Class IIb

A DES may be considered for clinical and anatomic settings in which the effectiveness/safety profile appears favorable but has not been fully confirmed by clinical trials. *(Level of Evidence: C)*

Management strategies for in-stent restenosis

Drug-eluting stents for the management of in-stent restenosis

Class IIa

It is reasonable to perform repeat PCI for in-stent restenosis with a DES or a new DES for patients who develop in-stent restenosis if anatomic factors are appropriate. *(Level of Evidence: B)*

Radiation for restenosis

Class IIa

Brachytherapy can be useful as a safe and effective treatment for ISR (in-stent restenosis). *(Level of Evidence: A)*

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. *(Level of Evidence: B)*

2 In chronic kidney disease patients undergoing angiography, isosmolar contrast agents are indicated and are preferred. *(Level of Evidence: A)*

Comparison with other guidelines

The only comparable guidelines are the European Society of Cardiology's (ESC) 2005 Guidelines for PCI [29]. There are differences in categories of recommendation, which makes direct comparison of the guidelines difficult. Specifically, the ESC guidelines have no class of recommendation III, and for class of recommendation I, they indicate that for the stated recommendation, there is general agreement or evidence that the therapy is beneficial, useful, or effective, but they do not say that it should be

performed or given. Within the limitation of comparison given these differences in wording of recommendations, there are no major variations in recommendations for the use of PCI or adjunctive therapies. The ESC guidelines do not include recommendations for secondary prevention with their PCI guidelines.

Ongoing research efforts and future directions

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial [30] comparing treatment with PCI and optimal medical therapy to optimal medical therapy alone in patients with stable angina was published after the inclusion deadline for the 2007 PCI Focused Update. Therefore, its findings are not included in the evidence base for these guidelines. Currently, the guideline for treatment of patients with chronic stable angina is undergoing an update, and if evidence from the COURAGE trial or similar studies should result in a change in recommendations, the PCI guidelines will be updated as well. Several studies are now under way to investigate the risk and appropriateness of therapy to prevent late stent thrombosis. Evidence from these trials may result in an update of current recommendations. Finally, studies involving the use of adjunctive therapies for patients undergoing PCI, especially newer antiplatelet medications, could result in a change in the current guideline recommendations.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: Percutaneous and Minimally Invasive Valve Procedures, http://circ.ahajournals.org/cgi/content/full/117/13/1750.

7 Coronary Artery Bypass Graft Surgery

Cullen D. Morris, Kim Eagle, Robert A. O'Rourke, and Robert A. Guyton

Background
Management recommendations in the reduction of perioperative mortality and morbidity
Preventing adverse cerebral outcomes
Ascending aortic atherosclerosis
Atrial fibrillation and postoperative stroke
Recent anterior MI, LV mural thrombus, and stroke risk
Recent antecedent cerebrovascular accident (CVA)
CPB time and neurologic risk
Carotid disease and neurological risk reduction
Other techniques to reduce neurologic risk
Reducing risk of perioperative myocardial dysfunction
Myocardial protection for patients with satisfactory preoperative cardiac function
Myocardial protection for patients with acutely depressed cardiac function
Myocardial protection for chronically dysfunctional myocardium
Cardiac biomarker elevation and outcome
Adjuncts to myocardial protection
Reoperative patients
Inferior infarct with right ventricular (RV) involvement
Attenuation of the systemic sequelae of CPB
Reducing the risk of perioperative infection
Prevention of postoperative arrhythmias
Strategies to reduce perioperative bleeding and transfusion
General management considerations
Maximizing postoperative benefit
Antiplatelet therapy for SVG patency
Pharmacologic management of hyperlipidemia
Hormonal manipulation
Smoking cessation
Cardiac rehabilitation
Special patient subsets
CABG in the elderly: age 70 and older
CABG in women
CABG in patients with diabetes
CABG in patients with pulmonary disease, COPD, or respiratory insufficiency
CABG in patients with end-stage renal disease (ESRD)
Valve disease
Reoperation
Concomitant PVD
Poor left ventricular function
Transplant patients
CABG in acute coronary syndromes
Impact of evolving technology
Less-invasive CABG
Robotics
Arterial and alternate conduits
Transmyocardial laser revascularization
Institutional and operator competence
Volume considerations
Report cards and quality improvement
Hospital environment
Economic issues
Cost-effectiveness of CABG
Cost comparison with angioplasty
Indications
Asymptomatic or mild angina
Stable angina
Unstable angina/non-ST segment elevation MI (NSTEMI)
ST-segmental elevation MI (STEMI)
Poor LV function
Life-threatening ventricular arrhythmias
CABG after failed PTCA
Patients with previous CABG
Future guidelines

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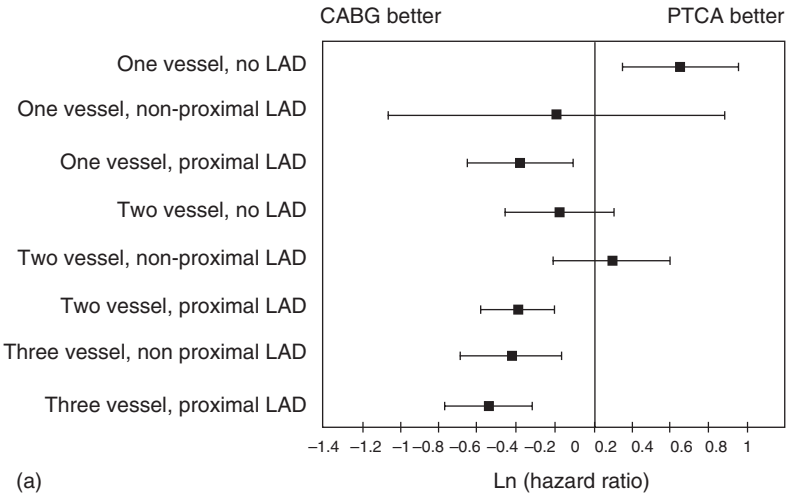

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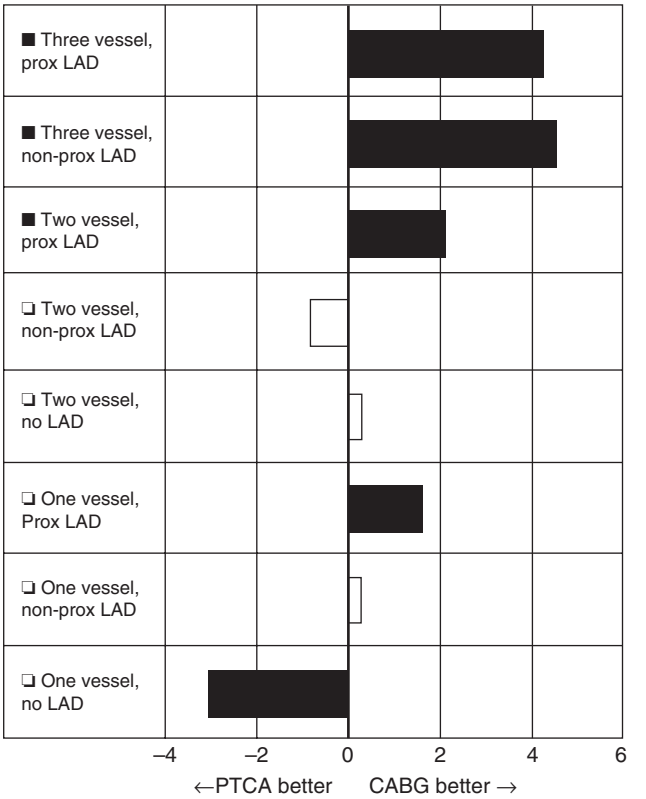

(b)

Fig. 7.1 A, 95% Confidence interval for ln (adjusted hazard ratio) of PTCA patient death: CABG patient death within a 3-year period (excluding patients with myocardial infarction less than 24 hours before the procedure). For the sample size within each anatomic cohort. **B**, Differences in adjusted percent survival at 3 years: percent CABG survival minus percent PTCA survival. Solid bars show statistically significant differences. Prox indicates proximal; LAD, left anterior descending coronary artery; PTCA, percutaneous coronary angioplasty; CABG, coronary artery bypass graft. Reprinted with permission from Elsevier Science, Inc. (Hannan *et al.* J Am Coll Cardiol. 1999;33:63–72).

Background

Surgical revascularization for obstructive coronary atherosclerotic heart disease (CASHD) offers relief of angina, improvement in exercise tolerance, and survival benefit [1]. Dedicated efforts over the last thirty years aimed at seeking effective treatment for the most common killer of humans in Western society led to an eventual recognition of the value of coronary artery bypass graft surgery (CABG). Through three large, prospectively randomized multicenter trials and several smaller studies, practitioners learned that patients with triple-vessel disease, left main disease, and CASHD with left ventricular (LV) dysfunction found benefit from surgery relative to medical therapy. Results from these studies led to the application of CABG to increasingly sicker patients.

Improvements in surgical and anesthetic techniques have evolved such that the expected 30-day mortality for elective CABG in the patient less than 65 years old with normal LV function is less than 1%. Progress has also been swift in the moderation of perioperative morbidity, particularly central nervous system (CNS) injury, the systemic insults of cardiopulmonary bypass (CPB), infection, bleeding, and renal function.

Nine randomized trials comparing surgery to percutaneous transluminal coronary angioplasty (PTCA) suggested that CABG provided better relief of angina with a reduced need for subsequent procedures [1]. Late death and rate of myocardial infarction were decreased in treated patients with diabetes mellitus who underwent CABG [1]. Data from large registries, particularly those of New York State, suggest that patients with severe, proximal LAD stenosis and/or triple-vessel disease may achieve improved survival with CABG (Fig. 7.1; Table 7.1). [1]. Since completion of these trials, however, improvements in PTCA (i.e., stent design and use, drug-eluting stents), surgery (more frequent use of arterial grafts), and post-procedural medical therapy have occurred.

Analysis of risk stratification in CABG has identified seven core variables (i.e., urgency of operation,

Table 7.1 Three-year survival by treatment in each anatomic subgroup

Coronary anatomy group		Survival			
		Patients (n)	Observed (%)	Adjusted (%)	*P*
1-Vessel, no LAD	CABG	507	89.2	92.4	0.003
	PTCA	11,233	95.4	95.3	
1-Vessel, nonproximal LAD	CABG	153	95.8	96.0	0.857
	PTCA	4130	95.7	95.7	
1-Vessel, proximal LAD	CABG	1917	95.8	96.6	0.010
	PTCA	5868	95.5	95.2	
2-Vessel, no LAD	CABG	1120	91.0	93.0	0.664
	PTCA	2729	93.4	92.6	
2-Vessel, nonproximal LAD	CABG	850	91.3	92.3	0.438
	PTCA	2300	93.3	93.1	
2-Vessel, proximal LAD	CABG	7242	93.5	93.8	<0.001
	PTCA	2376	92.8	91.7	
3-Vessel, nonproximal LAD	CABG	1984	90.1	90.3	0.002
	PTCA	660	86.7	86.0	
3-Vessel, proximal LAD	CABG	15,873	90.1	90.3	<0.001
	PTCA	634	88.2	86.1	

LAD indicates left anterior descending coronary artery; CABG, coronary artery bypass graft; and PTCA, percutaneous transluminal coronary angioplasty.

Comparative observed and adjusted 3-year survival of patients treated with PTCA or CABG in various anatomic subgroups.

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age, prior heart surgery, sex, LV ejection fraction (LVEF), percent stenosis of left main, and number of major coronaries with >70% stenosis) as being predictive of mortality [2]. Variables relating to urgency of operation, age, and prior CABG demonstrated the greatest predictive power. While elderly patients face an increased morbidity and mortality risk after CABG [3,4], age itself should not exclude a patient from being offered CABG, assuming there is no prohibitive comorbidity [1]. Early mortality after CABG continues to be associated particularly with advancing age, poor LV functions, and the urgency of operation [1].

CABG in the presence of or immediately after an acute myocardial infarction (MI) is controversial [1] and deserves special comment. Some believe that myocardium can be salvaged if operation is carried out within six hours of the onset of chest pain [5–8]. Percutaneous coronary intervention (PCI) appears to be the preferable first-line mode of therapy in the presence of an evolving MI. CABG is appropriate for patients with evidence of ongoing ischemia despite PCI, persistent angina, or intractable ventricular arrhythmias [6]. CABG during an evolving acute MI may also be performed coincident with repair of mechanical complications of an infarction (i.e., ventricular free wall rupture, ventricular septal defect, or papillary muscle rupture). CABG may also benefit patients with shock complicating a recent acute MI [9].

The American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) created a committee to establish guidelines for optimal surgical management of CASHD. The committee was composed of representatives of the ACC, AHA, and the ESC.

Management recommendations in the reduction of perioperative mortality and morbidity

Preventing adverse cerebral outcomes

Ascending aortic atherosclerosis

Class I

Significant atherosclerosis of the ascending aorta mandates a surgical approach that will minimize the possibility of arteriosclerotic emboli. (*Level of Evidence: C)*

The surgeon's identification of an atherosclerotic ascending aorta is the single most significant marker for an adverse cerebral outcome after coronary bypass operations [10]. Most perioperative cerebral atheroembolization likely arises intraoperatively from manipulation of the ascending or transverse aorta during cannulation, clamping, or placement of proximal anastomoses [11–13]. An aggressive approach to managing patients with severely atherosclerotic ascending aortas identified most accurately by intraoperative, surgeon-controlled epivascular ultrasound of the ascending aorta and arch appears to reduce the risk of postoperative stroke [14,15]. Important in this discussion is a potentially small population of patients who have such extensive aortic atherosclerosis that CABG would offer very little benefit [16], although this population is difficult to define. Alternative means of surgical revascularization, including off-pump CABG (OPCAB) and hybrid procedures should be explored for some of these high-risk patients. The relative value of OPCAB surgery in such patients remains unknown [1].

Atrial fibrillation and postoperative stroke

Class IIa

In post-CABG atrial fibrillation (AF) that is recurrent or persists more than 24 hours, warfarin anticoagulation for four weeks is probably indicated. (*Level of Evidence: C)*

New-onset AF occurs in 30% of patients undergoing CABG [1], with the peak incidence on the second postoperative day. It is associated with a 2- to 3- fold increase in postoperative risk for stroke [17]. Most strokes in this circumstance arise from thrombus that develops in the left atrial appendage.

Recent anterior MI, LV mural thrombus, and stroke risk

Class IIa

Long-term (3–6 months) anticoagulation is probably indicated for the patient with recent anteroapical infarct and persistent wall-motion abnormality after CABG. (*Level of Evidence: C)*

Class IIb

In patients having a recent anterior MI, preoperative screening with echocardiography may be considered to detect LV thrombus, because the technical

approach and timing of surgery may be altered. (*Level of Evidence: C)*

Recent antecedent cerebrovascular accident (CVA)

Occurrence of a recent, preoperative CVA presents a situation where delay in CABG may reduce perioperative neurologic risk [1]. A hemorrhagic component to the CVA is particularly important, as extension of the injury can result from heparinization required for CABG [18]. It is generally believed that a delay of 4 weeks or more is prudent if symptoms and coronary anatomy permit [1].

CPB time and neurologic risk

Increased time on CPB is associated with greater neurologic risk. Patients without neurologic injury have shorter pump times than those who develop stroke and/or type 2 events [19].

Carotid disease and neurological risk reduction

Class IIa

1 Carotid endarterectomy is probably recommended before CABG or concomitant to CABG in patients with symptomatic carotid stenosis or in asymptomatic patients with unilateral or bilateral internal carotid stenosis of 80% or more. (*Level of Evidence: C)*

2 Carotid screening is probably indicated in the following circumstances: age greater than 65, left main coronary stenosis, peripheral vascular disease, history of smoking, history of transient ischemic attack (TIA) or CVA, or a carotid bruit on physical examination. (*Level of Evidence: C)*

Hemodynamically significant carotid stenoses are associated with as many as 30% of postoperative strokes [20]. These strokes occur commonly on the second to ninth postoperative day during an apparent smooth postoperative recovery [21]. In the cardiac surgery population, up to 22% of patients have 50% carotid stenosis, and up to 12% have 80% carotid stenosis [22]. Perioperative stroke risk is 2% when carotid stenoses are less than 50%, 10% when stenoses are 50–80%, and 11–18.8% when carotid stenoses are greater than 80% [14,23].

Carotid endarterectomy done before or concomitant with CABG carries a low mortality (3.5%), reduces early postoperative stroke risk to less than 4%, and confers a 10-year rate of freedom from stroke of 88% to 96% [24,25]. The *staged* approach to carotid and CABG is most commonly employed, with carotid endarterectomy preceding CABG [1]. Postoperative care after carotid surgery occurs in a telemetry setting, with CABG following in 1 to 5 days later [1]. The superiority of combined versus staged has not been established by prospective trials. Stroke risk appears to be increased with a reversed-stage procedure, with CABG preceding carotid endarterectomy [26]. The reversed-stage procedure should be reserved for the uncommon patient with a true CABG emergency [1].

Other techniques to reduce neurologic risk

Since the number of microemboli delivered during an operation using CPB correlates with postoperative neurologic decline [27], the use of a 40-micron arterial line filter appears to be protective. Routine use of the membrane oxygenator over the bubble oxygenator is also encouraged [19,28,29]. The return of shed mediastinal blood to the CPB circuit via cardiotomy suction may increase the microembolic load to the brain [1]. OPCAB may reduce the incidence of neurologic injury by avoiding aortic manipulation [30], but reports have been mixed [31,32]. Alpha-stat acid/base management during CPB appears to be beneficial over pH-stat for CABG [31]. Finally, avoidance of cerebral hyperthermia [1], keeping blood return temperature below 38°C during rewarming [1], and maintaining serum normoglycemia are important adjuncts [1,35,36].

Reducing risk of perioperative myocardial dysfunction

Myocardial protection for patients with satisfactory preoperative cardiac function

There are a number of acceptable techniques associated with excellent results for the majority of patients undergoing CABG, and this is especially true in the case of normal, or preserved left ventricular function [1].

Myocardial protection for patients with acutely depressed cardiac function

Class I

Blood cardioplegia should be considered in patients undergoing CPB accompanying urgent/emergent

CABG for acute MI or unstable angina. (*Level of Evidence: B)* [1,36].

Myocardial protection for chronically dysfunctional myocardium

Class IIa

Blood cardioplegia is probably indicated in patients undergoing CPB accompanying CABG in the presence of a chronically dysfunctional left ventricle. (*Level of Evidence: B)* [1].

Cardiac biomarker elevation and outcome

Class IIb

Assessment of cardiac biomarkers in the first 24 hours after CABG may be considered, and patients with the highest elevations of creatine kinase-MB (greater than five times upper limits of normal) are at increased risk of subsequent events. (*Level of Evidence: B)*

Up to 90% of patients after CABG have some elevation of CK-MB [37], however marked elevation of CK-MB (5–10 times the upper limit of normal) is associated with an adverse prognosis [1]. The prognostic value of troponins after CABG is not as clearly defined, but some data show that Troponin T is more discriminatory than CK-MB [38]. Specific attention to optimal medical therapy with antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and statins should be given to the postoperative CABG patient with elevated biomarkers [1].

Adjuncts to myocardial protection

Class IIa

The use of prophylactic intra-aortic balloon pump as an adjunct to myocardial protection is probably indicated in patients with evidence of ongoing myocardial ischemia and/or patients with a subnormal cardiac index. (*Level of Evidence: B)*

The benefit of preoperative IABP placement in high-risk patients has been demonstrated [9], and the insertion of the IABP immediately prior to surgery in these patients afforded similar protection to that accompanying placement the day before CABG [39,40].

In addition to the long-term survival benefit offered by use of the IMA as a conduit in CABG, reduction in immediate operative mortality is also achieved by its use in all subgroups analyzed in the STS database, including the acutely ischemic patient and the elderly [1,7,42,43]. The only subgroup found to have similar outcomes between use/nonuse of the IMA is the patient older than 70 undergoing reoperative elective or nonelective CABG [1].

Reoperative patients

The use of retrograde cardioplegia techniques may allow for reduction in atheroembolism from patent/stenotic vein grafts encountered in reoperative cases [1].

Inferior infarct with right ventricular (RV) involvement

Class IIa

After infarction that leads to clinically significant RV dysfunction, it is reasonable to delay surgery for 4 weeks to allow recovery. (*Level of Evidence: C)*

RV failure secondary to ischemia, infarction, or stunning, presents a hazardous situation [7]. This patient typically has an occluded right coronary artery proximal to major RV branches and presents with an acute inferior infarction [1]. RV failure may or may not be immediately recognized. In this situation, a high index of suspicion for RV dysfunction must be raised. Physical examination of the neck veins, monitoring of the central venous pressure (CVP), electrocardiographic RV lead placement, or echocardiography should be employed [1,44,45]. There is substantial risk in operating on a patient after 4–6 hours of the onset of myocardial infarction in a patient with RV dysfunction [1]. Recovery of RV function usually occurs at 4 weeks after injury [46]. The nonsurgical postinfarction patient can most often be supported with pacing, volume loading, and judicious inotropic administration [47]. In the surgical setting, the RV is more difficult to manage, largely secondary to loss of pericardial constraint which allows acute dilatation of the RV [48]. In this situation, the RV often fails to recover despite revascularization, state-of-art myocardial protection, and ventricular assistance [1,48]. If early PCI of the right coronary is indicated, it should be performed [9].

Attenuation of the systemic sequelae of CPB

Glucocorticoid administration has demonstrated benefit in reducing the impact of the diffuse inflammatory response induced by CPB [1,49]. Although

there is no demonstration of increased risk of infection with glucocorticoids, it may be prudent to avoid administration in the diabetic patient [1]. Timing of administration and duration of treatment remain incompletely elucidated.

The serine protease inhibitor, aprotinin, has been withdrawn by the federal drug administration at the time of writing secondary to potential increased mortality risk demonstrated during a recent randomized study.

Perioperative leukocyte depletion prior to CABG performed with CPB may offer benefit, but concerns remain regarding thrombotic complications [50].

Reducing the risk of perioperative infection

Class I

1 Preoperative antibiotic administration should be used in all patients to reduce the risk of postoperative infection. (*Level of Evidence: A)*

2 In the absence of complicating circumstances, a deep sternal wound infection should be treated with aggressive surgical debridement and early revascularized muscle flap coverage. (*Level of Evidence: B)*

Class IIa

The risk for deep sternal wound infection is reduced by aggressive control of perioperative hyperglycemia by using a continuous, intravenous insulin infusion [51]. (*Level of Evidence: B)*

Skin and nasopharyngeal Gram-positive organisms are the leading cause of deep sternal wound infection or mediastinitis. Preoperative antimicrobial administration (within a 30–60 minute window prior to skin incision) reduces the risk of postoperative infection 5-fold [52]. The timing of administration is crucial [1]. If antibiotics are administered outside the 30–60 minute window, the beneficial effect is negated. The cephalosporin class is currently the agent of choice for infection prophylaxis in cardiac surgery [1]. Skin preparation with topical antiseptics, clipping hair instead of shaving, avoidance of hair removal, reduction of operating room traffic, laminar flow ventilation, shorter operations, minimal electrocautery, avoidance of bone wax, use of double-gloving barrier techniques for the operating team, and limiting homologous blood transfusions when possible have all been shown to reduce postoperative infection [1].

When sternal wound infection is identified, prompt aggressive treatment with debridement and muscle-flap closure is indicated [53].

Prevention of postoperative arrhythmias

Class I

Preoperative or early postoperative administration of beta-blockers in patients without contraindications should be used as the standard therapy to reduce the incidence and/or clinical sequelae of atrial fibrillation after CABG. (*Level of Evidence: B)*

Class IIa

1 Preoperative administration of amiodarone reduces the incidence of postcardiotomy atrial fibrillation and is an appropriate prophylactic therapy for patients at high risk for postoperative atrial fibrillation who have contraindications to therapy with beta-blockers. (*Level of Evidence: B)*

2 Digoxin and nondihydropyridine calcium-channel blockers are useful for control of ventricular rate but at present have no indication for prophylaxis. (*Level of Evidence: B)*

Class IIb

Low-dose sotalol can be considered to reduce the incidence of atrial fibrillation after CABG in patients who are not candidates for traditional beta-blockers. (*Level of Evidence: B)*

Postoperative atrial fibrillation increases the length of stay after CABG by up to 5 days, increases hospital charges, and is associated with a 2- to 3-fold increase in postoperative stroke [54,55]. If atrial fibrillation after CABG persists into a second day, warfarin anticoagulation with a goal of an international normalized ratio (INR) of 2.0 to 3.0 should be considered [56].

Strategies to reduce perioperative bleeding and transfusion

Predisposing risk factors for transfusion after CABG include advancing age, lower preoperative red blood cell volume, preoperative aspirin therapy, priority of operation, duration of CPB, recent fibrinolytic therapy, reoperative CABG, and differences in heparin management [1,57].

In certain patients in a appropriate clinical setting, including chronic stable angina, low-risk plaque morphology, and others, cessation of aspirin and

other platelet inhibitors 7 to 10 days before elective cardiac operations appears prudent to decrease the risk of postoperative bleeding and transfusion [1]. For clopidogrel, the recommendation is to discontinue the agent 5 or more days before surgery when the clinical situation will permit [1].

The serine protease inhibitor aprotinin with antifibrinolytic activity, significantly decreases postoperative blood loss and transfusion requirements in high-risk patients undergoing cardiac surgery [58,59]. However, aprotinin has been withdrawn from the market by the FDA secondary to increased mortality risk noted in a recent randomized study [124].

Epsilon-aminocaproic acid and tranexamic acid have antifibrinolytic activity, and both have been shown to decrease mediastinal drainage after cardiac surgery [60,61]. However, graft patency and thrombotic potential in post-CABG patients have not been resolved with either of these two agents [62].

Blood conservation during and after CABG is effective when using a multi-modality approach embracing individualized and algorithmically-driven techniques [63]. Both mechanical and pharmacologic means for blood conservation were used in a recent series of 100 consecutive elective patients undergoing CABG without a transfusion [64].

Prehospital autologous blood donation can be effective in reducing transfusion requirements if a patient is without exclusionary criteria (hemoglobin <12 mg/dL, heart failure, unstable angina, left main disease, or symptoms on the proposed day of donation) [1]. One to 3 U of autologous blood is donated over 30 days before operation. Alternatively, the patient and surgical team may opt to "donate" the patient's blood in the operating prior going on CPB. This blood is removed from the patient prior to an incision, and this blood is set aside, not exposed to the CPB circuitry. The autologous units of blood are reinfused into the patient after separation from CPB.

General management considerations

Acuteness of operation is an important determinant of operative risk. Prior to operative intervention, thought should be given to application of temporizing measures (i.e. pharmacologic therapy, IABP) when possible to improve the patient's condition prior to surgery [1]. Such concern is particularly important in the patient with pulmonary edema [1]. Ideally, operation is deferred until resolution of the edema [1].

Maximizing postoperative benefit

Antiplatelet therapy for SVG patency

Class I

Aspirin is the drug of choice for prophylaxis against early saphenous vein graft closure. It is the standard of care and should be continued indefinitely given its benefits in preventing subsequent clinical events. (*Level of Evidence: A)*

Aspirin therapy should be started within 48 hours of completing surgery, and this regimen has been shown to reduce mortality, MI, stroke, renal failure, and bowel infarction [65]. Ticlopidine offers no advantage over aspirin and life-threatening neutropenia is a rare but recognized side effect [1]. Clopidogrel offers a potential alternative to aspirin (in the truly aspirin allergic patient) with a similar side effect profile as aspirin [1]. Whether the combination of aspirin and clopidogrel is a superior regimen to either alone has not been resolved.

Pharmacologic management of hyperlipidemia

Class I

All patients undergoing CABG should receive statin therapy unless otherwise contraindicated. (*Level of Evidence: A)*

Statin therapy lowers low-density lipoprotein cholesterol (LDL-C) levels and retards atherosclerotic vein-graft disease [1].

Hormonal manipulation

Class III

Initiation of hormone therapy is not recommended for women undergoing CABG surgery. (*Level of Evidence: B)*

Smoking cessation

Class I

1 All smokers should receive educational counseling and be offered smoking cessation therapy after CABG. (*Level of Evidence: B)*

2 Pharmacologic therapy including nicotine replacement and buproprion should be offered to select patients indicating a willingness to quit. (*Level of Evidence: B)*

Smokers who quit successfully after CABG are rewarded with improved survival, improved graft patency, less recurrent angina, fewer hospital admissions, and better maintenance of employment over persistent smokers [66]. In addition, persistent smokers have more MIs and reoperations than those who stop smoking [67].

Cardiac rehabilitation

Class I

Cardiac rehabilitation should be offered to all eligible patients after CABG. (*Level of Evidence: B)*

Cardiac rehabilitation including early ambulation during hospitalization, outpatient prescriptive exercise training, family education, and sexual counseling have been shown to reduce mortality [1,68,69]. Outpatient rehabilitation beginning 4 to 8 weeks after CABG and consisting of three-times weekly educational and exercise sessions for 3 months is associated with an improvement in exercise tolerance and cholesterol levels [70].

Special patient subsets

CABG in the elderly: age 70 and older

Elderly patients have a higher incidence of left main disease, multivessel disease, LV dysfunction, and reoperation as the indication for surgery, and for many, concomitant valve surgery [1]. These patients also have more comorbid conditions and increased rates of fatal and nonfatal complications [71,72]. Operative mortality (%) is shown as a function of age in Fig. 7.2. A higher operative mortality occurs for all identified risk factors in patients aged 75 years or older than for those less than 65 [1]. Emergency surgery in the elderly confers up to a 10-fold increase in risk (3.5–35%), urgent surgery a 3-fold increase (3.5–15%), hemodynamic instability a 3- to 10-fold increase, and an LVEF <0.20 up to a 10-fold increase [1]. OPCAB may be advantageous in high-risk patients, particularly those with an LVEF less than 0.35 [73,74].

It should be emphasized that long-term survival and functional improvement can be achieved in the elderly patient despite severe cardiovascular disease and an urgent indication for surgery [75]. The 5-year survival of such patients who recover from surgery is comparable to that of the general population matched for age, sex, and race [76,77].

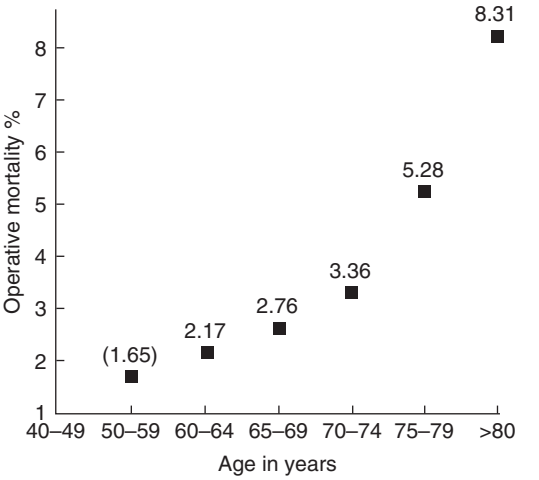

Fig. 7.2 Operative mortality (%) for CABG in various age cohorts. Data derived from Hannan *et al.* Am Heart J. 1994;128:1184–91.

Preoperative variables associated with poor long-term survival in elderly patients are atrial fibrillation, smoking, peripheral vascular disease, and poor renal function, and an unsatisfactory functional outcome has been influenced by hypertension, cerebrovascular insufficiency, and poor renal function [78]. Age alone should not be a contraindication to CABG if it is concluded that long-term benefits outweigh the procedural risk [1,79].

CABG in women

In-hospital mortality and morbidity and long-term survival after CABG appear related more to risk factors and patient characteristics than to gender, although some studies demonstrate increased risk for female low- and moderate-risk patients [80]. Women may be particularly vulnerable to postoperative congestive heart failure, low cardiac output syndrome [81–83], and blood loss [84]. However, CABG should not be delayed or denied to women who have the appropriate indication for revascularization [1].

CABG in patients with diabetes

Patients with diabetes have a higher mortality after MI and CABG than patients who do not have diabetes [1]. However, results from the BARI trial showed that patients with multivessel CASHD who were being for diabetes at baseline had a significantly better survival after CABG versus PTCA (Fig. 7.3)

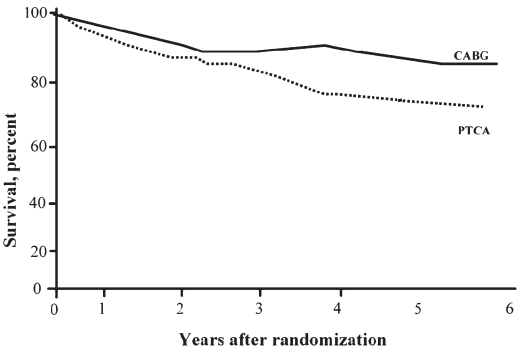

Fig. 7.3 Improved survival with coronary artery bypass graft surgery (CABG) versus percutaneous transluminal coronary angioplasty (PTCA) in patients with diabetes mellitus. Results from the Bypass Angioplasty Revascularization Investigation (BARI) showing that patients with multivessel coronary disease who were being treated for diabetes at baseline had a significantly better survival after coronary revascularization with CABG (solid curve) than with PTCA (dashed curve) ($P = 0.003$). Modified with permission from Circulation. 1997;96:1761–9.

[85]. The improved survival was limited to patients who were insulin-dependent and received an IMA graft during surgery.

Diabetic patients who are candidates for renal transplantation may have a particularly strong indication for CABG, as 20–30% of these patients have significant CASHD [86,87].

CABG in patients with pulmonary disease, COPD, or respiratory insufficiency

Postoperative respiratory dysfunction is common after CABG, and early extubation of patients after CABG is desirable. Longer periods of mechanical ventilation may be necessary in some patients who develop acute respiratory distress syndrome (ARDS), and in such patients, lower tidal volumes (6 mL/kg) should be considered [88].

The most common cause of preoperative pulmonary dysfunction is chronic obstructive pulmonary disease (COPD). A history of COPD has been reported as an independent risk factor for nosocomial pneumonia in patients after CABG [91]. Severity of COPD appears related to postoperative mortality, and patients with moderate-to-severe COPD are at increased risk after CABG [89,90]. Properly identifying the high-risk COPD patient is hampered by inconsistent reporting in the literature of the forced expiratory volume in the first second (FEV_1) in this subgroup. High-risk FEV_1 values range from less than 70% to less than 50% of the predicted normal values and/or an FEV_1 of less than 1.5 L in the literature. However, FEV_1 levels as low as 1.0 L would not necessarily disqualify a candidate for CABG [1]. Another indicator of risk is the degree of hypercapnea and the need for home oxygen therapy. Any elevated PCO_2 above the normal range on a preoperative arterial blood specimen renders the patient at least in the moderate-risk category, as does the need for home oxygen [1,90].

Preoperative efforts at improving pulmonary mechanics (i.e. incentive spirometer, bronchodilation, smoking cessation, chest physiotherapy, and antibiotics for lung infections) may diminish postoperative complications [1].

CABG in patients with end-stage renal disease (ESRD)

CABG may be offered to patients on dialysis with similar indications to patients without ESRD [1]. Dialysis patients are at increased but acceptable risks of perioperative mortality and morbidity (mediastinitis and stroke) after CABG, and CABG in these patients offers an increase in the quality of life for long-term survivors [1,92].

Valve disease

Class I

Patients undergoing CABG who have severe aortic stenosis (mean gradient greater than or equal to 50 mm Hg or Doppler velocity greater than or equal to 4 m/s) who meet the criteria for valve replacement should have concomitant aortic valve replacement (AVR). *(Level of Evidence: B)*

Class IIa

1 For a preoperative diagnosis of clinically significant mitral regurgitation, concomitant mitral correction at the time of coronary bypass is probably indicated. *(Level of Evidence: B)*

2 In patients undergoing CABG who have moderate aortic stenosis and are at acceptable risk for aortic valve replacement (mean gradient 30–50 mm Hg or Doppler velocity 3–4 m/s) concomitant aortic valve replacement is probably indicated. (*Level of Evidence: B*)

Class IIb

Patients undergoing CABG who have mild aortic stenosis (mean gradient less than 30 mm Hg or Doppler velocity less than 3 m/s) may be considered candidates for aortic valve replacement if risk of the combined procedure is acceptable. *(Level of Evidence: C)*

The incidence of CASHD in patients with angina pectoris who are undergoing AVR for aortic stenosis is 40% to 50% and drops to 20% in patients without chest pain [93,94]. The incidence of CASHD in patients with aortic insufficiency is less than that seen with aortic stenosis [93]. Mitral stenosis patients coming for valve surgery rarely have CASHD, as this lesion is seen most frequently in middle-age women [1].

Mitral regurgitation (MR) occurring with structurally normal leaflets in patients with CASHD is usually caused by ischemia to the left ventricle causing papillary muscle-induced leaflet tethering [1]. Intervention on the mitral valve in these instances is predicated on the findings on preoperative and intraoperative transesophageal echocardiography and size of the left atrium. With 1+ – 2+ MR and a left atrium of normal size (<4.5 cm), revascularization should proceed without direct valve inspection and intervention [1]. If the MR is 3+ – 4+ and the left atrium is enlarged, mitral valve repair is encouraged in addition to CABG [1]. Controversy exists somewhat in the case of ischemic moderate MR with normal leaflet morphology and a normal-sized left atrium [95,96].

The operative mortality for patients undergoing AVR who have ungrafted CASHD (lesions ≥50% on arteriography) approaches 10%, while those patients having AVR and concomitant CABG for CASHD have an operative mortality approaching that of AVR alone [97].

It is generally agreed that the risk of adding CABG to a valve operation increases the operative mortality over that of an isolated valve procedure. The addition of a valve operation to a CABG increases operative risk and risk of stroke [98].

Reoperation

Mortality rates for reoperative CABG are greater than that for primary surgery. However, reoperative CABG is often the best treatment strategy for many patients with recurrent myocardial ischemia. To date, no randomized studies comparing treatment options for patients with previous bypass surgery exist. Observational studies have demonstrated that reoperation improved the survival rate and symptom status of patients with late vein graft stenoses, particularly if a stenotic vein graft subtended the LAD coronary artery [1,99]. Other studies have identified a positive stress test as a factor that incrementally defines a group of patients at high risk without repeat surgery [1,99]. PCI of late (>5 years old) atherosclerotic vein grafts is less successful than in native coronaries with atherosclerosis [1].

The use of the IMA to LAD appears to decrease reoperative rates, and vein graft failure may be delayed by platelet inhibitors and statin therapy [99].

Concomitant PVD

The presence of clinical and subclinical PVD is a strong predictor of increased in-hospital and long-term mortality rate in patients undergoing CABG [1]. The coexistence of PVD and CASHD is well-established; patients undergoing peripheral vascular surgery should be screened for CASHD [1].

Poor left ventricular function

LV function is an important predictor of early and late mortality after CABG. Studies demonstrate mortality rates in patients with depressed LV function undergoing CABG exceeding the risk of CABG in patients with normal LV function by 2- to 3-fold [1,100–102]. However, the beneficial effects of surgical revascularization in the patient with ischemic heart disease and LV dysfunction are clearly evident when compared with medical treatments in terms of symptom relief, exercise tolerance, and long-term survival [100,103,104]. CABG is recommended in patients with severe multivessel disease and poor ventricular function but with a large amount of viable myocardium [1].

Transplant patients

Typically, CABG is not a good option for transplanted hearts with transplant vasculopathy because of the diffuse, distal involvement of the process [105]. Retransplantation is the only definitive therapy for advanced allograft vasculopathy [1].

The safety and efficacy of CABG in renal and liver transplanted patients has been described [106,107].

CABG in acute coronary syndromes

Class I

If clinical circumstances permit, clopidogrel should be withheld for 5 days before performance of CABG surgery. *(Level of Evidence: B)*

Acute coronary syndromes (ACS) represent a continuum from severe angina to acute MI. The most recent nomenclature defines the spectrum of ACS from unstable angina to non-ST-segment elevation MI (NSTEMI) to ST-segment elevation MI (STEMI). CABG offers a survival advantage over medical therapy in patients with unstable angina and LV dysfunction, particularly in those patients with triple-vessel disease [1]. In patients with coronary disease anatomy suitable for either PCI or CABG as treatments, there is no survival advantage of either treatment technique over the other [1].

Impact of evolving technology

Less-invasive CABG

OPCAB potentially offers less risk to the patient undergoing CABG. Three randomized, prospective trials have been reported comparing OPCAB and standard CABG using CPB. None of these trials were large enough to demonstrate any difference in operative mortality or the occurrence of postoperative stroke [108–110]. Larger randomized trials will be necessary to determine the subsets of patients receiving the most benefit from OPCAB.

Robotics

Closed chest multiarterial bypass on the beating heart would potentially offer the maximum benefit via the least invasive approach. The major obstacle to a totally endoscopic approach to CABG has been the technical difficulty in the construction of an accurate anastomosis.

Arterial and alternate conduits

Class I

In every patient undergoing CABG, the left IMA should be given primary consideration for revascularization of the LAD artery. *(Level of Evidence: B)*

Prospective angiographic studies from BARI documented an 87% 1-year vein patency rate compared with 98% for the IMA. The prospective study of vein graft patency noted a 66% patency rate at 10 postoperative years. Evidence that bilateral IMA (BIMA) usage provides incremental patency benefit over IMA plus vein grafts has been difficult to find. Concerns regarding operative difficulty, operative length of time, and increased wound infection rates have prevented universal acceptance of BIMA grafting. The radial artery as a conduit has seen interest in some centers. The potential for conduit vasospasm with the radial when exposed to catecholamines has caused some to avoid this strategy. Acar *et al.* reported an 84% 5-year radial patency rate in 100 consecutive patients receiving the radial artery as a bypass conduit during CABG [11]. Long-term results of the gastroepiploic and inferior epigastric arteries are not available; however, these arteries have been used with some success in the short term.

Transmyocardial laser revascularization

Class IIa

Transmyocardial surgical laser revascularization (TMLR), either alone or in combination with CABG is reasonable in patients with angina refractory to medical therapy who are not candidates for PCI or surgical revascularization. *(Level of Evidence: A)*

The principal utility of TMLR is directed towards patients with severe angina pectoris refractory to medical therapy and who are unsuitable for surgical revascularization, PCI, or heart transplantation. These patients often have small, diffusely diseased coronaries that are not amenable to CABG or PCI. Five prospective, randomized, controlled trials have demonstrated significant improvement in angina versus medical therapy with TMLR [112–116]. No trial demonstrated a survival benefit. The beneficial effects of TMLR seem to decline somewhat after one year [117].

Institutional and operator competence

Volume considerations

Studies suggest that survival after CABG is negatively affected when carried out in institutions that perform fewer than 100 cases annually [1].

Report cards and quality improvement

Outcome reporting in the form of risk-adjusted mortality rates after CABG has been effective in reducing mortality rates nationwide [1]. Public release of hospital and physician-specific mortality

rates has not been shown to drive the improvement in mortality. Furthermore, such reporting has failed to effectively guide consumers or alter clinicians' referral practices [1].

Hospital environment

Strategies to ensure consistent excellent care in patients undergoing coronary surgery have evolved. The most effective strategies include establishing specialized heart centers, forming multidisciplinary teams in hospitals, and creating and implementing pathways, algorithms, and specific protocols developed with surgeon input. Well-designed clinical pathways assist in delivering care by optimizing resource utilization, minimizing chance of error, and allowing for the reinvention of these standards within the context of local culture [1].

Economic issues

Cost-effectiveness of CABG

CABG is cost-effective in the subgroups of patients in whom survival and symptomatic benefit is demonstrable (Table 7.2). The most reasonable system of analysis for cost-effectiveness of CABG is an estimation of the dollars spent per quality-adjusted life year gained ($/QALY), and a cost-effectiveness of $20 000 to $40 000/QALY is consistent with other medical programs funded by society, such as hemodialysis and hypertension treatment [1].

Table 7.2 Cost per quality-adjusted life-year ($/QALY) of revascularization compared with medical therapy*

CABG for left main stenosis, with or without angina	9,000
CABG for 3VD with or without angina	18,000
CABG for 2VD with severe angina and LAD stenosis	22,000
CABG for 2VD with severe angina, no LAD disease	61,000
CABG for 2VD, no angina, with LAD stenosis	27,000
CABG for 2VD, no angina, no LAD disease	680,000
CABG for 1VD, severe angina	73,000
PTCA for 1VD, severe angina	9,000
PTCA for LAD stenosis, mild angina	92,000

CABG indicates coronary artery bypass graft; 1, 2, or 3VD, 1-, 2-, or 3-vessel disease; LAD, left anterior descending coronary artery; and PTCA, percutaneous transluminal coronary angioplasty.

*Adjusted to 1993 dollars from multiple sources in a review by Kupersmith *et al*. Prog Cardiovasc Dis. 1995;37:307–56.

Cost comparison with angioplasty

The initial cost of angioplasty is 50% to 65% of the initial cost of CABG. The incremental cost of repeated procedures during the follow-up period had led to a cumulative cost of angioplasty that approaches the cumulative of CABG at three years [1]. The use of drug-eluting stents will require a re-evaluation of cost-effectiveness considerations. The initial procedure is more expensive than angioplasty, sometimes approaching CABG in many patients with multivessel disease [1].

Indications

Asymptomatic or mild angina

Class I

1 CABG should be performed in patients with asymptomatic or mild angina who have significant left main coronary artery stenosis. *(Level of Evidence: A)*

2 CABG should be performed in patients with asymptomatic or mild angina who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. *(Level of Evidence: A)*

3 CABG is useful in patients with asymptomatic ischemia or mild angina who have 3-vessel disease. (Survival benefit is greater in patients with abnormal LV function; e.g., EF less than 0.50 and/or large areas of demonstrable myocardial ischemia.) *(Level of Evidence: C)*

Class IIa

CABG can be beneficial for patients with asymptomatic or mild angina who have proximal LAD stenosis with 1- or 2-vessel disease. (This recommendation becomes a Class I if extensive ischemia is documented by noninvasive study and/or LVEF is less than 0.50.) *(Level of Evidence: A)*

Class IIb

CABG may be considered for patients with asymptomatic or mild angina who have 1- or 2-vessel disease not involving the proximal LAD. (If a large area of viable myocardium and high-risk criteria are

met on noninvasive testing, this recommendation becomes Class I.) *(Level of Evidence: B)*

For patients without symptoms or with mild angina, the use of CABG is based on a survival advantage compared with nonsurgical therapy. A significant coronary stenosis is defined in the Guidelines as greater than or equal to a 50% reduction in lumen width on a 2-dimensional arteriogram, unless otherwise specified [1]. The indication for CABG in this category relates to the extent of coronary disease, the demonstration of objective signs or symptoms of this disease, and consideration for the risk of nonmedical therapy.

Stable angina

Class I

1 CABG is recommended for patients with stable angina who have significant left main coronary artery stenosis. *(Level of Evidence: A)*

2 CABG is recommended for patients with stable angina who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. *(Level of Evidence: A)*

3 CABG is recommended for patients with stable angina who have 3-vessel disease. (Survival benefit is greater when LVEF less than 0.50.) *(Level of Evidence: A)*

4 CABG is recommended in patients with stable angina who have 2-vessel disease with significant proximal LAD stenosis and either EF less than 0.50 or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)*

5 CABG is beneficial for patients with stable angina who have 1- or 2-vessel CASHD without significant proximal LAD stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*

6 CABG is beneficial for patients with stable angina who have developed disabling angina despite maximal noninvasive therapy, when surgery can be performed with acceptable risk. If angina is not typical, objective evidence of ischemia should be obtained. *(Level of Evidence: B)*

Class IIa

1 CABG is reasonable in patients with stable angina who have proximal LAD stenosis with 1-vessel disease. (This recommendation becomes Class I if extensive ischemia is documented by noninvasive study and/or LVEF is less than 0.50.) *(Level of Evidence: A)*

2 CABG may be useful for patients with stable angina who have 1- or 2-vessel CASHD without significant proximal LAD stenosis but who have a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing. *(Level of Evidence: B)*

Class III

1 CABG is not recommended for patients with stable angina who have 1- or 2-vessel disease not involving significant proximal LAD stenosis, patients who have mild symptoms that are unlikely due to myocardial ischemia, or patients who have not received an adequate trial of medical therapy and

a. have only a small area of viable myocardium or *(Level of Evidence: B)*

b. have no demonstrable ischemia on noninvasive testing. *(Level of Evidence: B)*

2 CABG is not recommended for patients with stable angina who have borderline coronary stenoses (50% to 60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing. *(Level of Evidence: B)*

3 CABG is not recommended for patients with stable angina who have insignificant coronary stenosis (less than 50% diameter reduction). *(Level of Evidence: B)*

In patients with stable angina (angina not severe enough to warrant surgery on grounds of symptoms alone), extension of patient survival has been demonstrated with CABG versus medical treatment, particularly in patients with left main disease, triple-vessel disease, and 1- or 2-vessel disease including LAD CASHD (Figure 7.4) [125]. The improvement in survival is also important for patients with abnormal exercise tests, more severe angina, higher clinical risk scores, and abnormal LV function (Figure 7.4) [125].

Unstable angina/non-ST segment elevation MI (NSTEMI)

Class I

1 CABG should be performed for patients with unstable angina/NSTEMI with significant left main coronary artery stenosis. *(Level of Evidence: A)*

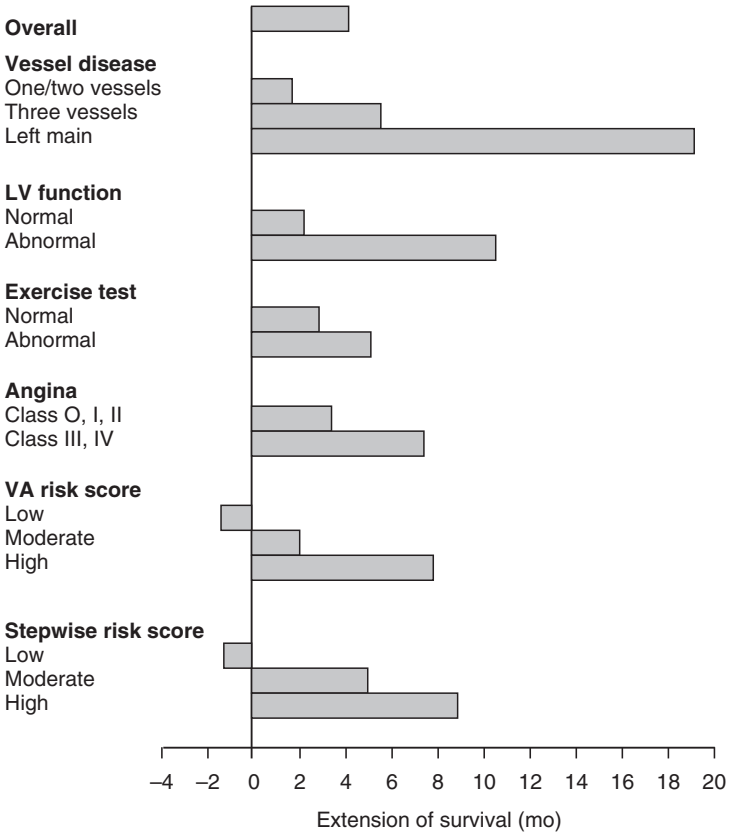

Fig. 7.4 Extension of survival after 10 years of follow-up in various subgroups of patients, from a meta-analysis of seven randomized studies. LV indicates left ventricular; VA, Veterans Administration. Reprinted with permission from Elsevier Science, Inc. (Yusuf *et al.* Lancet. 1994;344:563–70).

2 CABG should be performed for patients with unstable angina/NSTEMI who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. *(Level of Evidence: A)*

3 CABG is recommended for unstable angina/NSTEMI in patients in whom percutaneous revascularization is not optimal or possible, and who have ongoing ischemia not responsive to maximal nonsurgical therapy. *(Level of Evidence: B)*

Class IIa

CABG is probably indicated for patients with unstable angina/NSTEMI who have proximal LAD stenosis with 1- or 2-vessel disease. *(Level of Evidence: A)*

Class IIb

CABG may be considered in patients with unstable angina/NSTEMI who have 1- or 2-vessel disease not involving the proximal LAD when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria are met on noninvasive testing, this recommendation becomes Class I.) *(Level of Evidence: B)*

Timing of surgery is a critical issue is this category. In the patient in whom stablilization with aggressive medical therapy may be achieved, it is advisable to stabilize and reduce ongoing ischemia before proceeding to CABG. A small randomized trial demonstrated that insertion of an IABP 2 hours or more before CPB can reduce bypass time, intubation time, and length of stay, as well as improve

postoperative cardiac output in high-risk patients [118].

ST-segmental elevation MI (STEMI)

Class I

Emergency or urgent CABG in patients with STEMI should be undertaken in the following circumstances:

a. Failed angioplasty with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery. *(Level of Evidence: B)*

b. Persistent or recurrent ischemia refractory to medical therapy in patients who have coronary anatomy suitable for surgery, who have a significant area of myocardium at risk, and who are not candidates for PCI. *(Level of Evidence: B)*

c. At the time of surgical repair of postinfarction ventricular septal rupture or mitral valve insufficiency. *(Level of Evidence: B)*

d. Cardiogenic shock in patients less than 75 years old with ST-segment elevation or left bundle-branch block or posterior MI who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of patient's wishes or contraindications/unsuitability for further invasive care. *(Level of Evidence: A)*

e. Life-threatening ventricular arrhythmias in the presence of greater than or equal to 50% left main stenosis and/or triple vessel disease. *(Level of Evidence: B)*

Class IIa

1 CABG may be performed as primary reperfusion in patients who have suitable anatomy and who are not candidates for or who have had failed fibrinolysis/PCI and who are in the early hours (6 to 12 hours) of evolving STEMI. *(Level of Evidence: B)*

2 In patients who have had an STEMI or NSTEMI, CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. Beyond 7 days after infarction, the criteria for revascularization described in previous sections are applicable. *(Level of Evidence: B)*

Class III

1 Emergency CABG should not be performed in patients with persistent angina and a small area of myocardium at risk who are hemodynamically stable. *(Level of Evidence: C)*

2 Emergency CABG should not be performed in patients with successful microvascular reperfusion. *(Level of Evidence: C)*

The decision to perform emergent CABG requires angiographic demonstration of adequate target vessels in the region of infarction and usually other regions of myocardium also. Early CABG for acute infarction is appropriate only in patients with residual ongoing ischemia despite nonsurgical therapy. Specific conditions that warrant emergency CABG during an acute MI are left main stenosis, severe 3-vessel disease, associated valve disease (whether secondary to MI or unrelated) [119], and anatomy unsuitable for other forms of therapy [1].

Mechanical complications of acute MI include ventricular septal defect, MR secondary to papillary muscle infarction and/or rupture, and LV free wall rupture. There is general agreement that cardiogenic shock associated with a mechanical complication of an acute MI merits emergency operation to correct the defect as a life-saving procedure [1]. For stable patients with a mechanical complication, there is less clear documentation regarding timing of surgery [1].

Poor LV function

Class I

1 CABG should be performed in patients with poor LV function who have significant left main coronary artery stenosis. *(Level of Evidence: B)*

2 CABG should be performed in patients with poor LV function who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. *(Level of Evidence: B)*

3 CABG should be performed in patients with poor LV function who have proximal LAD stenosis with 2- or 3-vessel disease. *(Level of Evidence: B)*

Class IIa

CABG may be performed in patients with poor LV function with significant viable noncontracting,

revascularizable myocardium and without any of the above anatomic patterns. *(Level of Evidence: B)*

Class III

CABG should not be performed in patients with poor LV function without evidence of intermittent ischemia and without evidence of significant revascularizable viable myocardium. *(Level of Evidence: B)*

Operation on patients with poor LV function is appropriate if the patient has signs or symptoms of intermittent ischemia and minimal or no CHF [1]. If the patient has prominent signs and symptoms of CHF with minimal angina, the decision to operate should be based on objective evidence of hibernating myocardium [120].

Life-threatening ventricular arrhythmias

Class I

1 CABG should be performed in patients with life-threatening ventricular arrhythmias caused by left main coronary artery stenosis. *(Level of Evidence: B)*

2 CABG should be performed in patients with life-threatening ventricular arrhythmias caused by 3-vessel CASHD. *(Level of Evidence: B)*

Class IIa

1 CABG is reasonable in bypassable 1- or 2-vessel disease causing life-threatening ventricular arrhythmias. (This becomes a Class I recommendation if the arrhythmia is resuscitated sudden cardiac death or sustained ventricular tachycardia.) *(Level of Evidence: B)*

2 CABG is reasonable in life-threatening ventricular arrhythmias caused by proximal LAD disease with 1- or 2-vessel disease. (This becomes a Class I recommendation if the arrhythmia is resuscitated sudden cardiac death or sustained ventricular tachycardia.) *(Level of Evidence: B)*

Class III

CABG is not recommended in ventricular tachycardia with scar and no evidence of ischemia. *(Level of Evidence: B)*

In general, CABG has been more effective in reducing episodes of ventricular fibrillation than ventricular tachycardia, because the mechanism of the latter arrhythmia usually involves re-entry with scarred endocardium rather than ischemia [1]. In addition to CABG, implantation of an implantable cardioverter-defibrillator may be necessary in cases of ventricular arrhythmias, since revascularization may not alleviate all of the factors contributing to the arrhythmias [1].

CABG after failed PTCA

Class I

1 CABG should be performed after failed PTCA in the presence of ongoing ischemia or threatened occlusion with significant myocardium at risk. *(Level of Evidence: B)*

2 CABG should be performed after failed PTCA for hemodynamic compromise. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to perform CABG after failed PTCA for a foreign body in crucial anatomic position. *(Level of Evidence: C)*

2 CABG can be beneficial after failed PTCA for hemodynamic compromise in patients with impairment of the coagulation system and without previous sternotomy. *(Level of Evidence: C)*

Class IIb

CABG can be considered after failed PTCA for hemodynamic compromise in patients with impairment of the coagulation system and with previous sternotomy. *(Level of Evidence: C)*

Class III

1 CABG is not recommended after failed PTCA in the absence of ischemia. *(Level of Evidence: C)*

2 CABG is not recommended after failed PTCA with inability to revascularize due to target anatomy or no-reflow state. *(Level of Evidence: C)*

In patients that require emergency CABG after failed PCI, the rate of complications remains substantial [121–123]. A coordinated approach and cooperative interaction between the cardiologist, cardiac surgeon, and anesthesiologist are necessary for the best possible outcome in these challenging cases [1].

Patients with previous CABG

Class I

1 CABG should be performed in patients with prior CABG for disabling angina despite optimal

nonsurgical therapy. (If angina is not typical, then objective evidence of ischemia should be obtained.) *(Level of Evidence: B)*

2 CABG should be performed in patients with prior CABG without patent bypass grafts but with Class I indications for surgery for native-vessel CASHD (significant left main coronary stenosis, left main equivalent, 3-vessel disease.) *(Level of Evidence: B)*

Class IIa

1 CABG is reasonable in patients with prior CABG and bypassable distal vessels with a large area of threatened myocardium by noninvasive studies. *(Level of Evidence: B)*

2 CABG is reasonable in patients who have prior CABG if atherosclerotic vein grafts with stenoses greater than 50% supplying the LAD coronary artery or large areas of myocardium are present. *(Level of Evidence: B)*

Hospital mortality is increased 3-fold with reoperative CABG compared with the primary operation [1]. Reoperation is typically reserved for relief of disabling symptoms or for compelling evidence of life-threatening areas of myocardium at risk quantified by noninvasive studies. In the patient with a patent IMA graft supplying the LAD and recurrent ischemia in other regions of the heart, reoperation poses an especially high risk secondary to potential irreparable damage to the patent IMA consequent to the reoperation. The potential loss of the IMA to the LAD in such a reoperation represents a major negative factor in the long-term therapy of that patient. This is cause for additional caution in the recommendation of a reoperation in a patient with a patent IMA graft.

Future guidelines

Techniques of coronary revascularization have evolved rapidly in the last six years with the advent of drug-eluting stents and more widespread use of CABG. Prospective trials comparing methods of revascularization in multivessel disease are in progress, but at present there is insufficient data available to make alterations in the ACC/AHA guidelines. The authors anticipate that data from these randomized trials will lead to reconsiderations of revascularization guidelines in the near future.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

8 Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

Lee A. Fleisher

Introduction
General approach to the patient
Stepwise approach to perioperative cardiac assessment
Recommendations
- Recommendations for preoperative noninvasive evaluation of left ventricular function
- Recommendations for preoperative resting 12-lead ECG
- Recommendations for noninvasive stress testing before noncardiac surgery
- Recommendations for preoperative coronary revascularization with coronary artery bypass grafting or percutaneous coronary intervention
- Recommendations for beta-blocker medical therapy
- Recommendations for statin therapy
- Recommendations for alpha-2 agonists
- Recommendation for preoperative intensive care monitoring
- Recommendation for use of volatile anesthetic agents
- Recommendation for prophylactic intraoperative nitroglycerin
- Recommendation for use of transesophageal echocardiography
- Recommendation for maintenance of body temperature
- Recommendations for perioperative control of blood glucose concentration
- Recommendations for perioperative use of pulmonary artery catheters

This is a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery.

Writing committee members
Lee A. Fleisher, MD, FACC, FAHA, Chair; Joshua A. Beckman, MD, FACC¶; Kenneth A. Brown, MD, FACC, FAHA†; Hugh Calkins, MD, FACC, FAHA‡; Elliott Chaikof, MD#; Kirsten E. Fleischmann, MD, MPH, FACC; William K. Freeman, MD, FACC*; James B. Froehlich, MD, MPH, FACC; Edward K. Kasper, MD, FACC; Judy R. Kersten, MD, FACC; Barbara Riegel, DNSc, RN, FAHA; John F. Robb, MD, FACC‖

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ACC/AHA task force members
Sidney C. Smith, Jr, MD, FACC, FAHA, Chair; Alice K. Jacobs, MD, FACC, FAHA, Vice Chair; Cynthia D. Adams, MSN, PhD, FAHA†; Jeffrey L. Anderson, MD, FACC, FAHA††; Elliott M. Antman, MD, FACC, FAHA**; Christopher E. Buller, MD, FACC; Mark A. Creager, MD, FACC, FAHA; Steven M. Ettinger, MD, FACC; David P. Faxon, MD, FACC, FAHA††; Valentin Fuster, MD, PhD, FACC, FAHA††; Jonathan L. Halperin, MD, FACC, FAHA††; Loren F. Hiratzka, MD, FACC, FAHA††; Sharon A. Hunt, MD, FACC, FAHA††; Bruce W. Lytle, MD, FACC, FAHA; Rick Nishimura, MD, FACC, FAHA; Joseph P. Ornato, MD, FACC††; Richard L. Page, MD, FACC, FAHA; Barbara Riegel, DNSc, RN, FAHA††; Lynn G. Tarkington, RN; Clyde W. Yancy, MD, FACC

* American Society of Echocardiography Official Representative.
† American Society of Nuclear Cardiology Official Representative.
‡ Heart Rhythm Society Official Representative.
§ Society of Cardiovascular Anesthesiologists Official Representative.
‖ Society for Cardiovascular Angiography and Interventions Official Representative.
¶ Society for Vascular Medicine and Biology Official Representative.
# Society for Vascular Surgery Official Representative.
** Immediate Past Chair.
†† Former Task Force member during this writing effort.

Recommendations for intraoperative and postoperative use of ST-segment monitoring
Recommendations for surveillance for perioperative MI
Other guidelines
Recent studies and future directions

Introduction

These guidelines represent an update to those published in 2002 and are intended for physicians and nonphysician caregivers who are involved in the preoperative, operative, and postoperative care of patients undergoing noncardiac surgery. They provide a framework for considering cardiac risk of noncardiac surgery in a variety of patient and surgical situations. The writing committee that prepared these guidelines strove to incorporate what is currently known about perioperative risk and how this knowledge can be used in the individual patient.

The overriding theme of this document is that intervention is rarely necessary to simply lower the risk of surgery unless such intervention is indicated irrespective of the preoperative context. The purpose of preoperative evaluation is not to give medical clearance but rather to perform an evaluation of the patient's current medical status; make recommendations concerning the evaluation, management, and risk of cardiac problems over the entire perioperative period; and provide a clinical risk profile that the patient, primary physician and nonphysician caregivers, anesthesiologist, and surgeon can use in making treatment decisions that may influence short- and long-term cardiac outcomes. No test should be performed unless it is likely to influence patient treatment. The goal of the consultation is the optimal care of the patient.

General approach to the patient

This guideline focuses on the evaluation of the patient undergoing noncardiac surgery who is at risk for perioperative cardiac morbidity or mortality. In patients with known CAD or the new onset of signs or symptoms suggestive of CAD, baseline cardiac assessment should be performed. In the asymptomatic patient, a more extensive assessment of history and physical examination is warranted in those individuals 50 years of age or older, because the evidence related to the determination of cardiac risk factors and derivation of a revised cardiac risk index occurred in this population [1]. Preoperative cardiac evaluation must therefore be carefully tailored to the circumstances that have prompted the evaluation and to the nature of the surgical illness. In patients in whom coronary revascularization is not an option, it is often not necessary to perform a noninvasive stress test. Under other, less urgent circumstances, the preoperative cardiac evaluation may lead to a variety of responses, including cancellation of an elective procedure.

If a consultation is requested, then it is important to identify the key questions and ensure that all of the perioperative caregivers are considered when providing a response. Once a consultation has been obtained, the consultant should review available patient data, obtain a history, and perform a physical examination that includes a comprehensive cardiovascular examination and elements pertinent to the patient's problem and the proposed surgery. A critical role of the consultant is to determine the stability of the patient's cardiovascular status and whether the patient is in optimal medical condition within the context of the surgical illness. The consultant may recommend changes in medication, suggest preoperative tests or procedures, or propose higher levels of care postoperatively. In general, preoperative tests are recommended only if the information obtained will result in a change in the surgical procedure performed, a change in medical therapy or monitoring during or after surgery, or a postponement of surgery until the cardiac condition can be corrected or stabilized.

The consultant must also bear in mind that the perioperative evaluation may be the ideal opportunity to effect the long-term treatment of a patient with significant cardiac disease or risk of such disease. The referring physician and patient should be informed of the results of the evaluation and implications for the patient's prognosis. It is the cardiovascular consultant's responsibility to ensure clarity of communication so that findings and impressions will be incorporated effectively into the patient's overall plan of care. This ideally would include direct communication with the surgeon, anesthesiologist, and other physicians, as well as frank discussion directly with the patient and, if appropriate, the family. The consultant should not use phrases such as "clear for surgery."

Table 8.1 Active cardiac conditions for which the patient should undergo evaluation and treatment before noncardiac surgery (Class I, Level of Evidence: B)

Condition	Examples
Unstable coronary syndromes	Unstable or severe angina* (CCS class III or IV)†
	Recent MI‡
Decompensated HF (NYHA functional class IV; worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block
	Mobitz II atrioventricular block
	Third-degree atrioventricular heart block
	Symptomatic ventricular arrhythmias
Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR greater than 100 beats per minute at rest)	
	Symptomatic bradycardia
	Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient greater than 40 mm Hg, aortic valve area less than 1.0 cm^2, or symptomatic)
	Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

* According to Campeau.

† May include "stable" angina in patients who are unusually sedentary.

‡ The American College of Cardiology National Database Library defines recent MI as more than 7 days but less than or equal to 1 month (within 30 days).

CCS indicates Canadian Cardiovascular Society; HF, heart failure; HR, heart rate; MI, myocardial infarction; NYHA, New York Heart Association.

Stepwise approach to perioperative cardiac assessment

There continues to be a group of active cardiac conditions that when present indicate major clinical risk. The presence of one or more of these conditions mandates intensive management and may result in delay or cancellation of surgery unless the surgery is emergent (Table 8.1).

Given the increasing use of the Revised Cardiac Risk Index, the committee chose to replace the intermediate-risk category with the clinical risk factors from the index, with the exclusion of the type of surgery, which is incorporated elsewhere in the approach to the patient [1]. Clinical risk factors include:

- history of heart disease
- history of compensated or prior heart failure
- history of cerebrovascular disease
- diabetes mellitus, and
- renal insufficiency.

A history of MI or abnormal Q waves by ECG is listed as a clinical risk factor, whereas an acute MI (defined as at least one documented MI 7 days or less before the examination) or recent MI (more than 7 days but less than or equal to one month before the examination) with evidence of important ischemic risk by clinical symptoms or noninvasive study is an active cardiac condition. This definition reflects the consensus of the ACC Cardiovascular Database Committee. Minor predictors are recognized markers for cardiovascular disease that have not been proven to independently increase perioperative risk, for example, advanced age (greater than 70 years), abnormal ECG (LV hypertrophy, left bundle-branch block, ST-T abnormalities), rhythm other than sinus, and uncontrolled systemic hypertension. The presence of multiple minor predictors might lead to a higher suspicion of CAD but is not incorporated into the recommendations for treatment.

Figure 8.1 presents in algorithmic form a framework for determining which patients are candidates for cardiac testing. Given the availability of this evidence, the Writing Committee chose to include the level of the recommendations and strength of evidence for many of the pathways.

Step 1: The consultant should determine the urgency of noncardiac surgery. In many instances, patient- or surgery-specific factors dictate an obvious strategy (e.g., emergent surgery) that may not allow for further cardiac assessment or treatment. In such cases, the consultant may function best by providing recommendations for perioperative medical management and surveillance.

Step 2: Does the patient have one of the active cardiac conditions or clinical risk factors listed in Table 8.1? If not, proceed to Step 3. In patients being considered for elective noncardiac surgery, the presence of unstable coronary disease, decompensated heart failure, or severe arrhythmia or valvular heart disease usually leads to cancellation or delay of surgery until the cardiac problem has been clarified and treated appropriately. Examples of unstable coronary syndromes include previous MI with evidence of important ischemic risk by clinical symptoms or noninvasive study, unstable or severe angina, and new or poorly controlled ischemia-mediated heart failure. Many patients in these circumstances are referred for coronary angiography to assess further therapeutic options. Depending on the results of the test or interventions and the risk of delaying surgery, it may be appropriate to proceed to the planned surgery with maximal medical therapy.

Step 3: Is the patient undergoing low-risk surgery? In these patients, interventions based on cardiovascular testing in stable patients would rarely result in a change in management, and it would be appropriate to proceed with the planned surgical procedure.

Step 4: Does the patient have a functional capacity greater than or equal to 4 METS without symptoms? In highly functional asymptomatic patients, management will rarely be changed on the basis of results of any further cardiovascular testing [2]. It is therefore appropriate to proceed with the planned surgery. In patients with known cardiovascular disease or at least one clinical risk factor, perioperative heart rate control with beta-blockade appears appropriate as outlined in Table 8.4.

If the patient has not had a recent exercise test, functional status can usually be estimated from the ability to perform activities of daily living. For this purpose, functional capacity has been classified as excellent (greater than 10 METs), good (7 to 10 METs), moderate (4 to 7 METs), poor (less than 4 METs), or unknown. The Duke Activity Status Index (Table 8.2) contains questions that can be used to estimate the patient's functional capacity [3].

Step 5: If the patient has poor functional capacity, is symptomatic, or has unknown functional capacity, then the presence of clinical risk factors will determine the need for further evaluation. If the patient has no clinical risk factors, then it is appropriate to proceed with the planned surgery, and no further change in management is indicated.

If the patient has one or two clinical risk factors, then it is reasonable either to proceed with the planned surgery or, if appropriate, with heart rate control with beta-blockade, or to consider testing if it will change management [4–6]. In patients with three or more clinical risk factors, the surgery-specific cardiac risk is important.

The surgery-specific cardiac risk (Table 8.3) of noncardiac surgery is related to two important factors. First, the type of surgery itself may identify a patient with a greater likelihood of underlying heart disease and higher perioperative morbidity and mortality. Perhaps the most extensively studied example is vascular surgery, in which underlying CAD is present in a substantial portion of patients [7]. If the patient is undergoing vascular surgery, recent studies suggest that testing should only be considered if it will change management [4–6,8]. Other types of surgery may be associated with similar risk to vascular surgery but have not been studied extensively. In nonvascular surgery in which the perioperative morbidity related to the procedures ranges from 1% to 5% (intermediate-risk surgery), there are insufficient data to determine the best strategy (proceeding with the planned surgery with tight heart rate control with beta-blockade or further cardiovascular testing if it will change management).

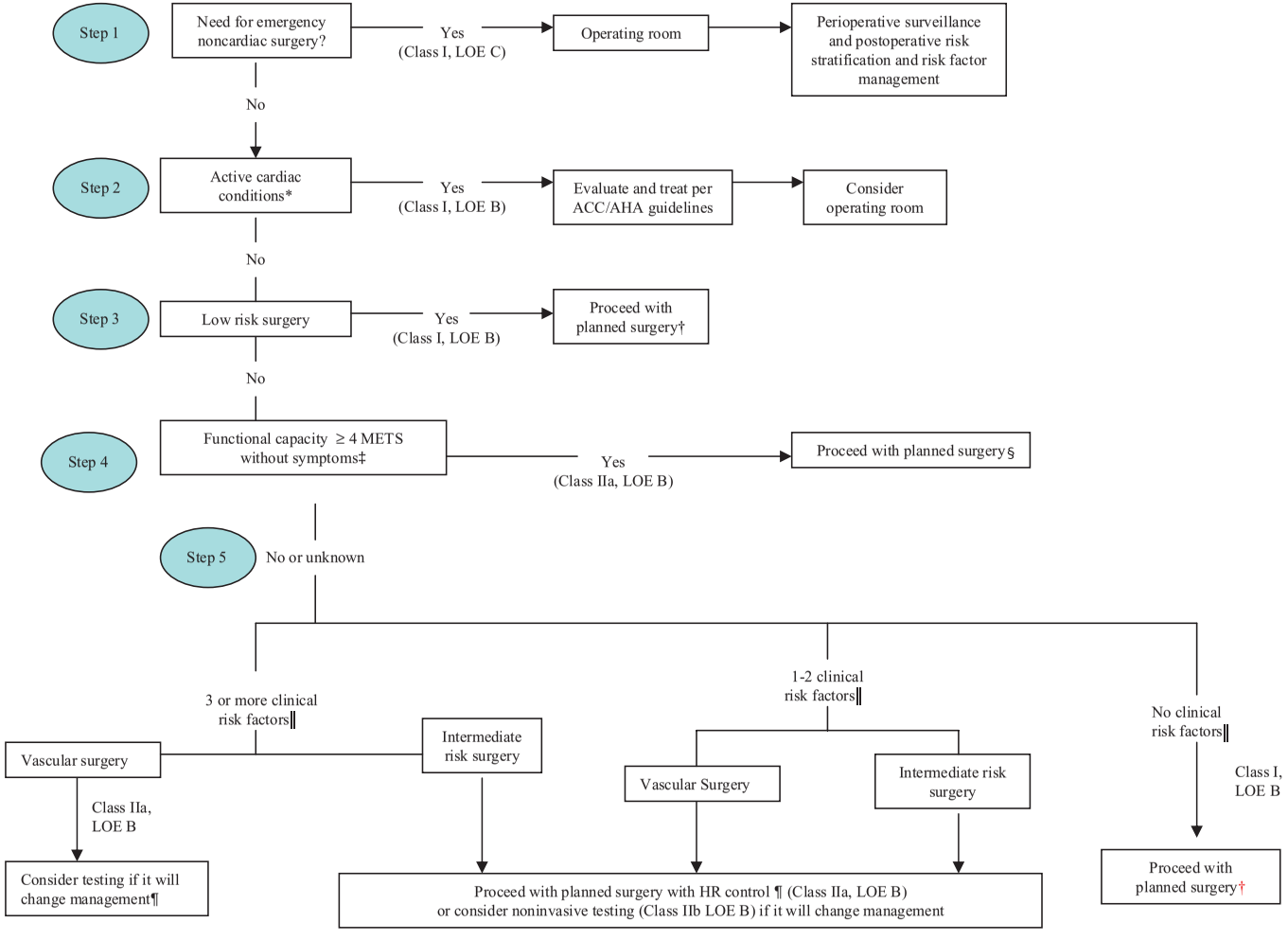


Fig. 8.1 Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or greater. *See Table 8.1 for active clinical conditions. †See Table 8.2 for estimated MET level equivalent. ‡Clinical risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. §Consider perioperative beta-blockade (see Table 8.4) for populations in which this has been shown to reduce cardiac morbidity/mortality. ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate; LOE, level of evidence; and MET, metabolic equivalent.

Table 8.2 Estimated energy requirements for various activities

	Can you . . .		Can you . . .
1 MET	Take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or two on level ground at 2 to 3 mph (3.2 to 4.8 kph)?	4 METs	Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph (6.4 kph)? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
4 METs	Do light work around the house like dusting or washing dishes?		Participate in moderate Recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
		Greater than 10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

kph indicates kilometers per hour; MET, metabolic equivalent; and mph, miles per hour.

Table 8.3 Cardiac risk* stratification for noncardiac surgical procedures

Risk stratification	Procedure examples
Vascular (reported cardiac risk often more than 5%)	Aortic and other major vascular surgery
Intermediate (reported cardiac risk generally 1% to 5%)	Peripheral vascular surgery Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low† (reported cardiac risk generally less than 1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and nonfatal myocardial infarction.

†These procedures do not generally require further preoperative cardiac testing.

Recommendations

Recommendations for preoperative noninvasive evaluation of left ventricular function

Class IIa

1 It is reasonable for patients with dyspnea of unknown origin to undergo preoperative evaluation of left ventricular (LV) function. *(Level of Evidence: C)*

2 It is reasonable for patients with current or prior heart failure with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function if not performed within 12 months. *(Level of Evidence: C)*

Class IIb

Reassessment of LV function in clinically stable patients with previously documented

cardiomyopathy is not well-established. *(Level of Evidence: C)*

Class III

Routine perioperative evaluation of LV function in patients is not recommended. *(Level of Evidence: B)*

Recommendations for preoperative resting 12-lead ECG

Class I

1 Preoperative resting 12-lead ECG is recommended for patients with at least one clinical risk factor* who are undergoing vascular surgical procedures. *(Level of Evidence: B)*

2 Preoperative resting 12-lead ECG is recommended for patients with known coronary heart disease, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures. *(Level of Evidence: C)*

Class IIa

Preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors who are undergoing vascular surgical procedures. *(Level of Evidence: B)*

Class IIb

Preoperative resting 12-lead ECG may be reasonable in patients with at least 1 clinical risk factor who are undergoing intermediate-risk operative procedures. *(Level of Evidence: B)*

Class III

Preoperative and postoperative resting 12-lead ECGs are not indicated in asymptomatic persons undergoing low-risk surgical procedures. *(Level of Evidence: B)*

Recommendations for noninvasive stress testing before noncardiac surgery [9]

Class I

Patients with active cardiac conditions (Table 8.1) in whom noncardiac surgery is planned should be evaluated and treated per ACC/AHA guidelines† before noncardiac surgery. *(Level of Evidence: B)*

Class IIa

Noninvasive stress testing of patients with three or more clinical risk factors and poor functional capacity (less than four metabolic equivalents [METs]) who require vascular surgery‡ is reasonable if it will change management. *(Level of Evidence: B)*

Class IIb

Noninvasive stress testing may be considered for patients with at least one to two clinical risk factors and poor functional capacity (less than 4 METs) who require intermediate-risk noncardiac or vascular surgery if it will change management. *(Level of Evidence: B)*

Class III

1 Noninvasive testing is not useful for patients with no clinical risk factors undergoing intermediate-risk noncardiac surgery. *(Level of Evidence: C)*

2 Noninvasive testing is not useful for patients undergoing low-risk noncardiac surgery. *(Level of Evidence: C)*

Recommendations for preoperative coronary revascularization with coronary artery bypass grafting or percutaneous coronary intervention [4–6,11–13]

See Figs 8.2 and 8.3.

(All of the Class I indications below are consistent with the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery [14].)

---

* Clinical risk factors include history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency.

† ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation (1), ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2), ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (3), ACC/AHA/ESC Guidelines for the Management of Patients With Supraventricular Arrhythmias (4), ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction (5), ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (6), and ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (7).

‡ Vascular surgery is defined by aortic and other major vascular surgery and peripheral vascular surgery. See Table 8.3.

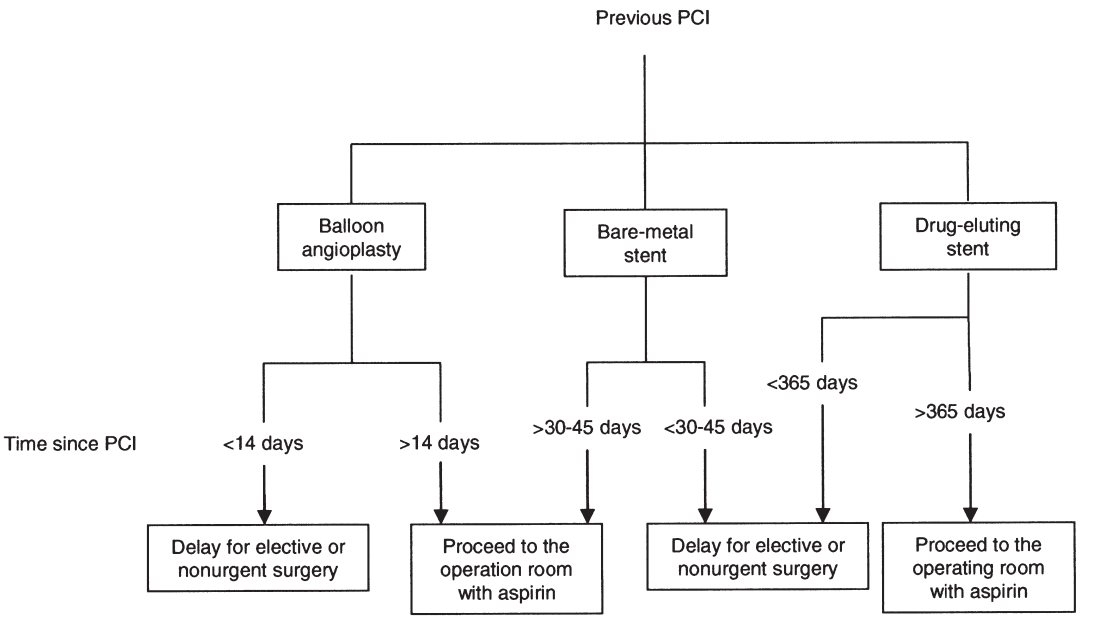
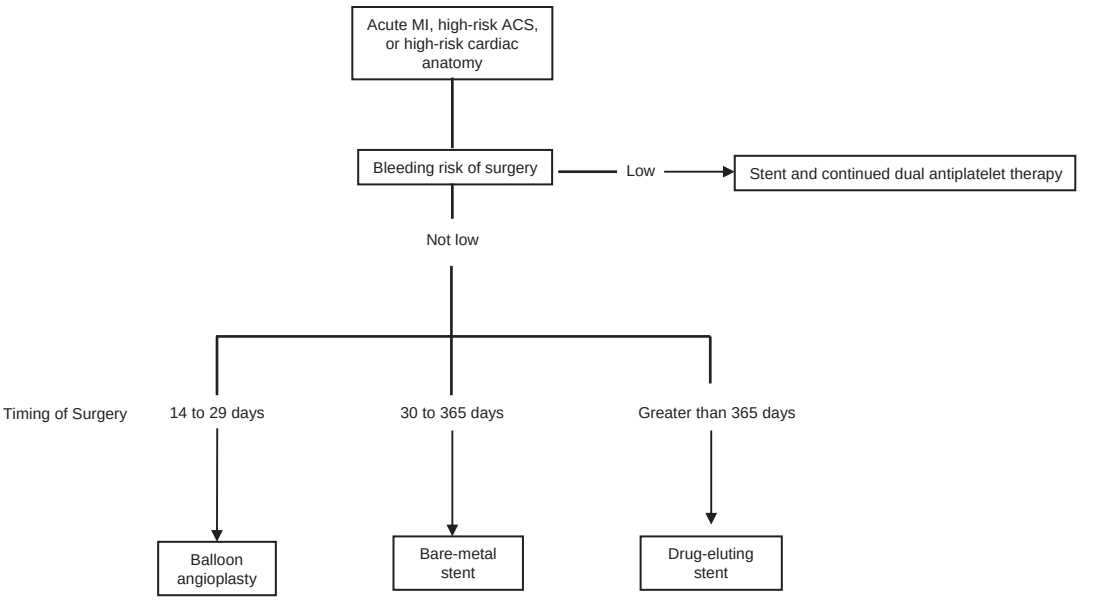


Fig. 8.2 Proposed approach to the management of patients with previous percutaneous coronary intervention (PCI) who require noncardiac surgery, based on expert opinion.



MI indicates myocardial infarction and ACS, acute coronary syndrome

Fig. 8.3 Treatment for patients requiring percutaneous coronary intervention who need subsequent surgery. ACS indicates acute coronary syndrome; COR, class of recommendation; LOE, level of evidence; and MI, myocardial infarction.

Class I

1 Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have significant left main coronary artery stenosis. *(Level of Evidence: A)*

2 Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 3-vessel disease. (Survival benefit is greater when left ventricular ejection fraction is less than 0.50.) *(Level of Evidence: A)*

3 Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 2-vessel disease with significant proximal left anterior descending stenosis and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)*

4 Coronary revascularization before noncardiac surgery is recommended for patients with high-risk unstable angina or non-ST-segment elevation myocardial infarction (MI).§ *(Level of Evidence: A)*

5 Coronary revascularization before noncardiac surgery is recommended in patients with acute ST-elevation MI. *(Level of Evidence: A)*

Class IIa

1 In patients in whom coronary revascularization with percutaneous coronary intervention (PCI) is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare-metal stent placement followed by 4 to 6 weeks of dual-antiplatelet therapy is probably indicated. *(Level of Evidence: B)*

2 In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. *(Level of Evidence: C)*

Class IIb

1 The usefulness of preoperative coronary revascularization is not well established in high-risk ischemic patients (e.g., abnormal dobutamine stress echocardiogram with at least five segments of wall-motion abnormalities). *(Level of Evidence: C)*

2 The usefulness of preoperative coronary revascularization is not well established for low-risk ischemic patients with an abnormal dobutamine stress echocardiogram (segments 1 to 4). *(Level of Evidence: B)*

Class III

1 It is not recommended that routine prophylactic coronary revascularization be performed in patients with stable coronary artery disease (CAD) before noncardiac surgery. *(Level of Evidence: B)*

2 Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy or aspirin and thienopyridine therapy will need to be discontinued perioperatively. *(Level of Evidence: B)*

3 Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. *(Level of Evidence: B)*

Recommendations for beta-blocker medical therapy‖ [15–20]

See Table 8.4

Class I

1 Beta-blockers should be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications. *(Level of Evidence: C)*

2 Beta-blockers should be given to patients undergoing vascular surgery who are at high cardiac risk owing to the finding of ischemia on preoperative testing. *(Level of Evidence: B)*

§ High-risk unstable angina/non-ST-elevation MI patients were identified as those with age greater than 75 years, accelerating tempo of ischemic symptoms in the preceding 48 hours, ongoing rest pain greater than 20 minutes in duration, pulmonary edema, angina with S_3 gallop or rales, new or worsening mitral regurgitation murmur, hypotension, bradycardia, tachycardia, dynamic ST-segment change greater than or equal to 1 mm, new or presumed new bundle-branch block on ECG, or elevated cardiac biomarkers, such as troponin.

‖ Care should be taken in applying recommendations on beta-blocker therapy to patients with decompensated heart failure, nonischemic cardiomyopathy, or severe valvular heart disease in the absence of coronary heart disease.

Table 8.4 Recommendations for perioperative beta-blocker therapy based on published randomized clinical trials

Surgery	No clinical risk factos	One or more clinical risk factors	CHD or high cardiac risk	Patients currently taking beta-blockers
Vascular	Class IIb, Level of Evidence: B	Class IIa, Level of Evidence: B	Patients found to have myocardial ischemia on preoperative testing: Class I, Level of Evidence B* Patients without ischemia or no previous test: Class IIa, Level of Evidence: B	Class I, Level of Evidence: B
Intermediate risk	–	Class IIb, Level of Evidence: C	Class IIa, Level of Evidence: B	Class I, Level of Evidence: C
Low risk	–	–	–	Class I, Level of Evidence: C

See Table 8.3 for definition of procedures. Dashes indicate that data were insufficient to determine a class of recommendation or level of evidence. See text for further discussion. CHD indicates coronary heart disease.

*Applies to patients found to have coronary ischemia on preoperative testing.

†Applies to patients found to have coronary heart disease.

Class IIa

1 Beta-blockers are probably recommended for patients undergoing vascular surgery in whom preoperative assessment identifies coronary heart disease. *(Level of Evidence: B)*

2 Beta-blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than one clinical risk factor. *(Level of Evidence: B)*

3 Beta-blockers are probably recommended for patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk, as defined by the presence of more than one clinical risk factor, who are undergoing intermediate-risk or vascular surgery. *(Level of Evidence: B)*

Class IIb

1 The usefulness of beta-blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery, in whom preoperative assessment identifies a single clinical risk factor. *(Level of Evidence: C)*

2 The usefulness of beta-blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta-blockers. *(Level of Evidence: B)*

Class III

Beta-blockers should not be given to patients undergoing surgery who have absolute contraindications to beta-blockade. *(Level of Evidence: C)*

Recommendations for statin therapy [21]

Class I

For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued. *(Level of Evidence: B)*

Class IIa

For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable. *(Level of Evidence: B)*

Class IIb

For patients with at least 1 clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered. *(Level of Evidence: C)*

Recommendations for alpha-2 agonists [22]

Class IIb

Alpha-2 agonists for perioperative control of hypertension may be considered for patients with known CAD or at least one clinical risk factor who are undergoing surgery. *(Level of Evidence: B)*

Class III
Alpha-2 agonists should not be given to patients undergoing surgery who have contraindications to this medication. *(Level of Evidence: C)*

Recommendation for preoperative intensive care monitoring

Class IIb
Preoperative intensive care monitoring with a pulmonary artery catheter for optimization of hemodynamic status might be considered; however, it is rarely required and should be restricted to a very small number of highly selected patients whose presentation is unstable and who have multiple comorbid conditions. *(Level of Evidence: B)*

Recommendation for use of volatile anesthetic agents

Class IIa
It can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia. *(Level of Evidence: B)*

Recommendation for prophylactic intraoperative nitroglycerin

Class IIb
The usefulness of intraoperative nitroglycerin as a prophylactic agent to prevent myocardial ischemia and cardiac morbidity is unclear for high-risk patients undergoing noncardiac surgery, particularly those who have required nitrate therapy to control angina. The recommendation for prophylactic use of nitroglycerin must take into account the anesthetic plan and patient hemodynamics and must recognize that vasodilation and hypovolemia can readily occur during anesthesia and surgery. *(Level of Evidence: C)*

Recommendation for use of transesophageal echocardiography [23]

Class IIa
The emergency use of intraoperative or perioperative transesophageal echocardiography is reasonable to determine the cause of an acute, persistent, and life-threatening hemodynamic abnormality. *(Level of Evidence: C)*

Recommendation for maintenance of body temperature [24]

Class I
Maintenance of body temperature in a normothermic range is recommended for most procedures other than during periods in which mild hypothermia is intended to provide organ protection (e.g., during high aortic cross-clamping). *(Level of Evidence: B)*

Recommendations for perioperative control of blood glucose concentration

Class IIa
It is reasonable that blood glucose concentration be controlled¶ during the perioperative period in patients with diabetes mellitus or acute hyperglycemia who are at high risk for myocardial ischemia or who are undergoing vascular and major noncardiac surgical procedures with planned intensive care unit admission. *(Level of Evidence: B)*

Class IIb
The usefulness of strict control of blood glucose concentration¶ during the perioperative period is uncertain in patients with diabetes mellitus or acute hyperglycemia who are undergoing noncardiac surgical procedures without planned intensive care unit admission. *(Level of Evidence: C)*

Recommendations for perioperative use of pulmonary artery catheters [25,26]

Class IIb
Use of a pulmonary artery catheter may be reasonable in patients at risk for major hemodynamic disturbances that are easily detected by a pulmonary artery catheter; however, the decision must be based on three parameters: patient disease, surgical procedure (i.e., intraoperative and postoperative fluid shifts), and practice setting (experience in pulmonary artery catheter use and interpretation of results), because incorrect interpretation of the data from a pulmonary artery catheter may cause harm. *(Level of Evidence: B)*

¶Blood glucose levels less than 150 mg/dL appear to be beneficial.

Class III

Routine use of a pulmonary artery catheter perioperatively, especially in patients at low risk of developing hemodynamic disturbances, is not recommended. *(Level of Evidence: A)*

Recommendations for intraoperative and postoperative use of ST-segment monitoring

Class IIa

Intraoperative and postoperative ST-segment monitoring can be useful to monitor patients with known CAD or those undergoing vascular surgery, with computerized ST-segment analysis, when available, used to detect myocardial ischemia during the perioperative period. *(Level of Evidence: B)*

Class IIb

Intraoperative and postoperative ST-segment monitoring may be considered in patients with single or multiple risk factors for CAD who are undergoing noncardiac surgery. *(Level of Evidence: B)*

Recommendations for surveillance for perioperative MI

Class I

Postoperative troponin measurement is recommended in patients with ECG changes or chest pain typical of acute coronary syndrome. *(Level of Evidence: C)*

Class IIb

The use of postoperative troponin measurement is not well established in patients who are clinically stable and have undergone vascular and intermediate-risk surgery. *(Level of Evidence: C)*

Class III

Postoperative troponin measurement is not recommended in asymptomatic stable patients who have undergone low-risk surgery. *(Level of Evidence: C)*

Other guidelines

Currently, the only other Guideline devoted to the subject was published in 1997 by Palda and Detsky for the American College of Physicians [27]. Given the decade since the publication of this Guideline, and the fact there has been significant new evidence since its publication, its recommendations require updating. There is currently a task force of the European Society of Cardiology on preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery, but Guidelines are still being developed.

Recent studies and future directions

Since publication of the Guidelines, the POISE study group reported on their randomized controlled trial of perioperative beta-blockers in 8351 patients with a history of coronary artery disease, peripheral artery disease, stroke, or congestive heart failure within the last three years; who were undergoing major vascular surgery; or who had three of the following seven risk factors: undergoing high-risk surgery, having a history of CHF, having diabetes mellitus, having renal insufficiency, being 70 years of age or older, having a history of transient ischemic attack, or undergoing urgent/emergent surgery [28].

Patients were recruited from 193 centers and were randomized to receive either metoprolol CR or placebo started two to four hours preoperatively and continued for 30 days. The dose of metoprolol administered was 100 mg in the preoperative period, 100 mg in the six-hour postoperative period, 200 mg 12 hours later, and 200 mg daily thereafter out to 30 days. The primary outcome included cardiovascular death, nonfatal MI, and nonfatal cardiac arrest by 30 days after randomization. Secondary outcomes included total mortality, cardiovascular death, MI, cardiac revascularization, clinically significant atrial fibrillation, clinically significant bradycardia, clinically significant hypotension, and stroke.

The investigators reported a significant reduction in the primary outcome in the metoprolol group (5.8% vs. 6.9%), with the major effect being a reduction in nonfatal myocardial infarction. Of note, the incidence of all cause mortality was significantly greater in the metoprolol group (3.1% vs. 2.3%, odds ratio 1.33, CI 1.03–1.74)) and stroke (1.0% vs. 0.5%, odds ratio 2.17, CI 1.26–3.74). There were no specific subgroups of patients who would achieve the greatest benefit compared to risk. Therefore, starting perioperative metoprolol in beta-blocker naïve patients the morning of surgery is associated

with major adverse effects, which most individuals believe would outweigh any positive effects. It is unknown if starting these agents at least 7 days before surgery would lead to lower rates of death or stroke, while maintaining the benefit for reducing perioperative MI, and further research is warranted.

In an accompanying commentary, Fleisher and Poldermans suggest that the higher rate of stroke and death in the metoprolol succinate may be related to the dose given in the trial [29]. They further suggest that for those patients with indications for perioperative β-blocker therapy, but in whom there is insufficient time to appropriately titrate the medication, the overriding theme is that tachycardia due to perioperative events, i.e. bleeding, hypovolemia, inadequate control of pain or infection, should not be initially treated with additional β-blocker but the underlying cause of these conditions should be treated first. If tachycardia persists, then they recommend that β-blocker can be used cautiously in high-risk patients with proven or suspected coronary artery disease, preferably supervised in the perioperative setting by physicians who have experience with perioperative hemodynamics such that hypotension and other hemodynamic aberrations which may have led to the increased incidence of stroke or septic death are avoided. The AHA/ACC Guideline Committee had not reviewed the trial to make a formal recommendation at the time of this publication.

There are several other major areas requiring further research. While the current Guidelines advocate continuing statin therapy in the perioperative period, further trials are needed to determine if starting statin therapy would be beneficial. Additionally, there is significant debate regarding the optimal perioperative management of patients with coronary stents. Specifically, information is needed on the safe time interval to wait before operating on patients with drug-eluting stents and the ideal management of anti-platelet agents. Finally, information is required to determine the optimal strategy to monitor patients for perioperative cardiac events and how this information should be utilized to inform long-term care.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

9 Lower Extremity Peripheral Artery Disease

Alan T. Hirsch and Ziv J. Haskal

Scope, organization of committee and evidence
Data standards and performance measures
Vascular history and physical examination
Epidemiology, prognosis, and natural history of PAD
Clinical presentations
- Asymptomatic PAD
- Claudication
- Critical limb ischemia
- Acute limb ischemia
- Prior limb arterial revascularization

Diagnostic methods
- Ankle-brachial and toe-brachial indices, and segmental pressure examination
- Treadmill exercise testing with and without ABI assessments and 6-minute walk test
- Duplex ultrasound
- Computed tomographic angiography
- Magnetic resonance angiography
- Contrast angiography

Treatment
- Cardiovascular risk reduction
  - *Lipid-lowering drugs*
  - *Antihypertensive drugs*
  - *Diabetes therapies*
  - *Smoking cessation*
  - *Antiplatelet and antithrombotic drugs*
- Claudication
  - *Exercise and lower extremity pad rehabilitation*
  - *Pharmacological therapy of claudication*
  - *Endovascular treatment for claudication*
  - *Surgery for claudication*
- Critical limb ischemia and treatment for limb salvage
  - *Medical and pharmacological treatment for CLI*
  - *Thrombolysis for acute and chronic limb ischemia*
  - *Surgery for CLI*

Other guidelines: The Trans-Atlantic Inter-Society Consensus Documents, TASC-I and TASC-II
Ongoing trials and future directions on PAD care

The AHA Guidelines and Scientific Statements Handbook
Edited by Valentin Fuster
ISBN: 978-1-405-18463-2

Scope, organization of committee and evidence

The "Guidelines for the Management of Patients with Peripheral Arterial Disease" address the diagnosis and management of atherosclerotic, aneurysmal, and thromboembolic peripheral arterial disease (PAD). The guideline uses the term "peripheral arterial disease" to encompass a large series of disorders that affect arteries exclusive of the coronary arteries. The writing committee chose to include within its scope the disorders of the abdominal aorta, renal and mesenteric arteries, and lower extremity arteries. This chapter is more limited and will review the recommendations encompassed in care for patients with lower extremity PAD. Clinicians who seek the highest possible practice standards and the evidence base underpinning these recommendations are strongly encouraged to refer to the full text document to gain access to the 65 tables, more than 1300 references, and supporting text. The full-text document can be accessed at http://www.acc.org/clinical/guidelines/pad/index.pdf [1].

These guidelines were written by representatives of the American College of Cardiology (ACC), the American Heart Association; the Society for Cardiovascular Angiography and Interventions (SCAI); Society for Vascular Medicine (SVM); Society for Vascular Surgery (SVS); and Society of Interventional Radiology (SIR). The document was peer reviewed by additional representatives of these organizations prior to approval, and also reviewed and

endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR); National Heart, Lung, and Blood Institute (NHLBI); Society for Vascular Nursing (SVN); TransAtlantic Inter-Society Consensus (TASC); and Vascular Disease Foundation (VDF). Thus, this guideline accurately reflects the national evidence base that should guide lower extremity PAD care.

Data standards and performance measures

Individuals with lower extremity peripheral artery disease are encumbered by illness that has high morbidity and mortality and whose contemporary outcomes remain suboptimal. Improvement in clinical outcomes cannot be achieved by an evidence-based guideline alone, and improved care standards are more likely to be achieved when the "process of care" aligns clinician intent within a supportive health system, so that prescribed actions can achieve measurable outcomes [2]. Thus, the ACC and collaborating societies will imminently publish a series of PAD "data standards" that will define the data definitions and measurable outcomes that can be encompassed within either electronic medical records or other data management systems [3]. As well, a set of PAD "performance measures" will be soon published that will define those key recommendations that should serve as definable guideposts of lower extremity PAD care excellence. Readers should seek these two publications when they are in press in 2009.

Vascular history and physical examination

Prior to the publication of this guideline, there was no evidence-based, consensus-driven, and common interdisciplinary approach to the collection of a vascular history or to the performance of a clinical examination. All clinicians, spanning primary care to specialty practices, should utilize a proactive collection of key vascular historical details. A common measurement of pulse intensity is now established.

Class I

1 Individuals at risk for lower extremity PAD should undergo a vascular review of symptoms to assess walking impairment, claudication, ischemic rest pain, and/or the presence of nonhealing wounds. *(Level of Evidence: C)*

2 Individuals at risk for lower extremity PAD should undergo comprehensive pulse examination and inspection of the feet. *(Level of Evidence: C)*

Key components of the vascular review of systems (not usually included in the review of systems of the extremities) and family history include the following:

- Any exertional limitation of the lower extremity muscles or any history of walking impairment. The characteristics of this limitation may be described as fatigue, aching, numbness, or pain. The primary site(s) of discomfort in the buttock, thigh, calf, or foot should be recorded, along with the relation of such discomfort to rest or exertion.
- Any poorly healing or nonhealing wounds of the legs or feet.
- Any pain at rest localized to the lower leg or foot and its association with the upright or recumbent positions.
- Postprandial abdominal pain that reproducibly is provoked by eating and is associated with weight loss.
- Family history of a first-degree relative with an abdominal aortic aneurysm.

Care should also be guided by performance of a focused vascular physical examination, which is detailed in Table 9.1.

Epidemiology, prognosis, and natural history of PAD

The major cause of lower extremity PAD is atherosclerosis. Risk factors for atherosclerosis such as cigarette smoking, diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia increase the likelihood of developing lower extremity PAD (Fig. 9.1). Lower extremity PAD is a common syndrome that affects a large proportion of most adult populations worldwide. Peripheral arterial disease is most often asymptomatic, but these individuals remain at high cardiovascular risk, and such individuals can be effectively detected by use of the ankle-brachial index measurement. Claudication, representing the primary symptom of lower extremity PAD, defines a significantly smaller subset of the total population

Table 9.1 The vascular physical examination

Key components of the vascular physical examination are as follows:

- Measurement of blood pressure in both arms and notation of any interarm asymmetry.
- Palpation of the carotid pulses and notation of the carotid upstroke and amplitude and presence of bruits.
- Auscultation of the abdomen and flank for bruits.
- Palpation of the abdomen and notation of the presence of the aortic pulsation and its maximal diameter.
- Palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial sites. Perform Allen's test when knowledge of hand perfusion is needed.
- Auscultation of both femoral arteries for the presence of bruits.
- Pulse intensity should be assessed and should be recorded numerically as follows: 0, absent; 1, diminished; 2, normal; and 3, bounding.
- The shoes and socks should be removed; the feet inspected; the color, temperature, and integrity of the skin and intertriginous areas evaluated; and the presence of ulcerations recorded.
- Additional findings suggestive of severe PAD, including distal hair loss, trophic skin changes, and hypertrophic nails, should be sought and recorded.

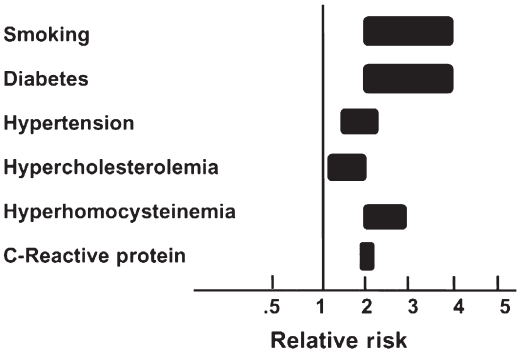


Fig. 9.1 Risk of developing lower extremity PAD.

with the disease. This guideline defines five distinct lower extremity clinical syndromes that should be used to guide the appropriateness of diagnostic and therapeutic efforts: Asymptomatic, atypical leg pain, claudication, chronic critical limb ischemia, and acute limb ischemia. Individuals with both chronic critical limb ischemia or acute limb ischemia represent a cohort with the highest cardiovascular morbidity and mortality, and for whom immediate vascular specialty care is always required. As well, one additional "clinical presentation" (prior limb arterial revascularization) is highlighted for care focus, recognizing that PAD is never "fixed" by any revascularization procedure. PAD care must deliberately continue after any individual revascularization "episode of care" via use of graft or PTA site surveillance and prescription of risk reduction therapies.

Table 9.2 Individuals at risk for lower extremity peripheral artery disease

- Age less than 50 years, with diabetes and one other atherosclerosis risk factor
- Age 50 to 69 years and history of smoking or diabetes
- Age 70 years and older
- Leg symptoms with exertion (suggestive of claudication) or ischemic rest pain
- Abnormal lower extremity pulse examination
- Known atherosclerotic coronary, carotid, or renal artery disease

Clinical presentations

Asymptomatic PAD

Class I

1 A history of walking impairment, claudication, ischemic rest pain, and/or nonhealing wounds is recommended as a required component of a standard review of systems for adults 50 years and older who have atherosclerosis risk factors and for adults 70 years and older. *(Level of Evidence: C)*

2 Individuals with asymptomatic lower extremity PAD should be identified by examination and/or measurement of the ankle-brachial index (ABI) so that therapeutic interventions known to diminish their increased risk of myocardial infarction (MI), stroke, and death may be offered. *(Level of Evidence: B)*

3 Smoking cessation, lipid lowering, and diabetes and hypertension treatment according to current national treatment guidelines are recommended for individuals with asymptomatic lower extremity PAD. *(Level of Evidence: B)*

4 Antiplatelet therapy is indicated for individuals with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular ischemic events. *(Level of Evidence: C)*

Class IIa

1 An exercise ABI measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD (Table 9.1) who have a normal ABI (0.91 to 1.30), are without classic claudication symptoms, and have no other clinical evidence of atherosclerosis. *(Level of Evidence: C)*

2 A toe-brachial index or pulse volume recording measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD who have an ABI greater than 1.30 and no other clinical evidence of atherosclerosis. *(Level of Evidence: C)*

Class IIb

Angiotensin-converting enzyme (ACE) inhibition may be considered for individuals with asymptomatic lower extremity PAD for cardiovascular risk reduction. *(Level of Evidence: C)*

Claudication

See Table 9.3.

Class I

1 Patients with symptoms of intermittent claudication should undergo a vascular physical examination, including measurement of the ABI. *(Level of Evidence: B)*

2 In patients with symptoms of intermittent claudication, the ABI should be measured after exercise if the resting index is normal. *(Level of Evidence: B)*

3 Patients with intermittent claudication should have significant functional impairment with a reasonable likelihood of symptomatic improvement and absence of other disease that would comparably limit exercise even if the claudication was improved (e.g., angina, heart failure, chronic respiratory disease, or orthopedic limitations) before undergoing an evaluation for revascularization. *(Level of Evidence: C)*

4 Individuals with intermittent claudication who are offered the option of endovascular or surgical therapies should (a) be provided information regarding supervised claudication exercise therapy and pharmacotherapy; (b) receive comprehensive risk factor modification and antiplatelet therapy; (c) have a significant disability, either being unable to perform normal work or having serious impairment of other activities important to the patient; and (d) have lower extremity PAD lesion anatomy such that the revascularization procedure would have low risk and a high probability of initial and long-term success. *(Level of Evidence: C)*

Table 9.3 Indications for revascularization in intermittent claudication

Before offering a patient with intermittent claudication the option of any invasive revascularization therapy, whether endovascular or surgical, the following considerations must be taken into account:

- A predicted or observed lack of adequate response to exercise therapy and claudication pharmacotherapies
- Presence of a severe disability, either being unable to perform normal work or having very serious impairment of other activities important to the patient
- Absence of other disease that would limit exercise even if the claudication was improved (e.g., angina or chronic respiratory disease)
- The individual's anticipated natural history and prognosis
- The morphology of the lesion (must be such that the appropriate intervention would have low risk and a high probability of initial and long-term success)

Class III

Arterial imaging is not indicated for patients with a normal post-exercise ABI. This does not apply if other causes (e.g., entrapment syndromes or isolated internal iliac artery occlusive disease) are suspected. *(Level of Evidence: C)*

Critical limb ischemia

See Tables 9.4 and 9.5.

Table 9.4 Objectives for diagnostic evaluation of patients with critical limb ischemia

The diagnostic evaluation of patients with critical limb ischemia should be directed toward the following objectives:

- Objective confirmation of the diagnosis
- Localization of the responsible lesion(s) and a gauge of relative severity
- Assessment of the hemodynamic requirements for successful revascularization (vis-à-vis proximal versus combined revascularization of multilevel disease)
- Assessment of individual patient endovascular or operative risk

Table 9.5 Differential diagnosis of common foot and leg ulcers

Original	Cause	Location	Pain	Appearance
Main arteries	Atherosclerotic lower extremity PAD, Buerger's disease, acute arterial occlusion	Toes, foot	Severe	Irregular, pink base
Venous	Venous disease	Malleolar	Mild	Irregular, pink base
Skin infarct	Systemic disease, embolism, hypertension	Lower third of leg	Severe	Small after infarction, often multiple
Neurotrophic	Neuropathy	Foot sole	None	Often deep, infected

Class I

1 Patients with CLI should undergo expedited evaluation and treatment of factors that are known to increase the risk of amputation. *(Level of Evidence: C)*

2 Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk. *(Level of Evidence: B)*

3 Patients with a prior history of CLI or who have undergone successful treatment for CLI should be evaluated at least twice annually by a vascular specialist owing to the relatively high incidence of recurrence. *(Level of Evidence: C)*

4 Patients at risk of CLI (ABI less than 0.4 in a nondiabetic individual, or any diabetic individual with known lower extremity PAD) should undergo regular inspection of the feet to detect objective signs of CLI. *(Level of Evidence: B)*

5 The feet should be examined directly, with shoes and socks removed, at regular intervals after successful treatment of CLI. *(Level of Evidence: C)*

6 Patients with CLI and features to suggest atheroembolization should be evaluated for aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms). *(Level of Evidence: B)*

7 Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection. *(Level of Evidence: B)*

8 Patients with CLI and skin breakdown should be referred to healthcare providers with specialized expertise in wound care. *(Level of Evidence: B)*

9 Patients at risk for CLI (those with diabetes, neuropathy, chronic renal failure, or infection) who develop acute limb symptoms represent potential vascular emergencies and should be assessed immediately and treated by a specialist competent in treating vascular disease. *(Level of Evidence: C)*

10 Patients at risk for or who have been treated for CLI should receive verbal and written instructions regarding self-surveillance for potential recurrence. *(Level of Evidence: C)*

Acute limb ischemia

Class I

Patients with acute limb ischemia and a salvageable extremity should undergo an emergent evaluation that defines the anatomic level of occlusion and that leads to prompt endovascular or surgical revascularization. *(Level of Evidence: B)*

Class III

Patients with acute limb ischemia and a nonviable extremity should not undergo an evaluation to define vascular anatomy or efforts to attempt revascularization. *(Level of Evidence: B)*

Prior limb arterial revascularization

See Table 9.6

Class I

Long-term patency of infrainguinal bypass grafts should be evaluated in a surveillance program, which should include an interval vascular history, resting ABIs, physical examination, and a duplex ultrasound at regular intervals if a venous conduit has been used. *(Level of Evidence: B)*

Class IIa

1 Long-term patency of infrainguinal bypass grafts may be considered for evaluation in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals. *(Level of Evidence: B)*

Table 9.6 Surveillance program for infrainguinal vein bypass grafts

Patients undergoing vein bypass graft placement in the lower extremity for the treatment of claudication or limb-threatening ischemia should be entered into a surveillance program. This program should consist of:

- Interval history (new symptoms)
- Vascular examination of the leg with palpation of proximal, graft, and outflow vessel pulses
- Periodic measurement of resting and, if possible, postexercise ABIs
- Duplex scanning of the entire length of the graft, with calculation of peak systolic velocities and velocity ratios across all identified lesions

Surveillance programs should be performed in the immediate postoperative period and at regular intervals for at least 2 years

- Femoral-popliteal and femoral-tibial venous conduit bypass at approximately 3, 6, and 12 months and annually

2 Long-term patency of endovascular sites may be evaluated in a surveillance program, which may include conducting exercise ABIs and other arterial imaging studies at regular intervals. *(Level of Evidence: B)*

Diagnostic methods

See Fig. 9.2.

Patients with lower extremity PAD can almost always be provided with an accurate anatomic diagnosis by use of modern noninvasive vascular diagnostic techniques (e.g., ankle- and toe-brachial indices, segmental pressure measurements, pulse volume recordings, duplex ultrasound imaging, Doppler waveform analysis, and exercise testing). These tests will usually provide adequate information for creation of a therapeutic plan. When required, these physiological and anatomic data can be supplemented by use of MRA and CTA studies and selective use of invasive aortic and lower extremity angiographic techniques. Every vascular clinician and most primary care providers should be aware of the relative accuracy, benefits and limitations of diagnostic technique.

Ankle-brachial and toe-brachial indices, and segmental pressure examination

Class I

1 The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with exertional leg symptoms, with nonhealing wounds, who are 70 years and older, or who are 50 years and older with a history of smoking or diabetes. *(Level of Evidence: C)*

2 The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline. *(Level of Evidence: B)*

3 The toe-brachial index should be used to establish the lower extremity PAD diagnosis in patients in whom lower extremity PAD is clinically suspected but in whom the ABI test is not reliable due to noncompressible vessels (usually patients with longstanding diabetes or advanced age). *(Level of Evidence: B)*

4 Leg segmental pressure measurements are useful to establish the lower extremity PAD diagnosis when anatomic localization of lower extremity PAD is required to create a therapeutic plan. *(Level of Evidence: B)*

Treadmill exercise testing with and without ABI assessments and 6-minute walk test

Class I

1 Exercise treadmill tests are recommended to provide the most objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy. *(Level of Evidence: B)*

2 A standardized exercise protocol (either fixed or graded) with a motorized treadmill should be used to ensure reproducibility of measurements of pain-free walking distance and maximal walking distance. *(Level of Evidence: B)*

3 Exercise treadmill tests with measurement of pre-exercise and postexercise ABI values are recommended to provide diagnostic data useful in differentiating arterial claudication from nonarterial claudication ("pseudoclaudication"). *(Level of Evidence: B)*

4 Exercise treadmill tests should be performed in individuals with claudication who are to undergo exercise training (lower extremity PAD

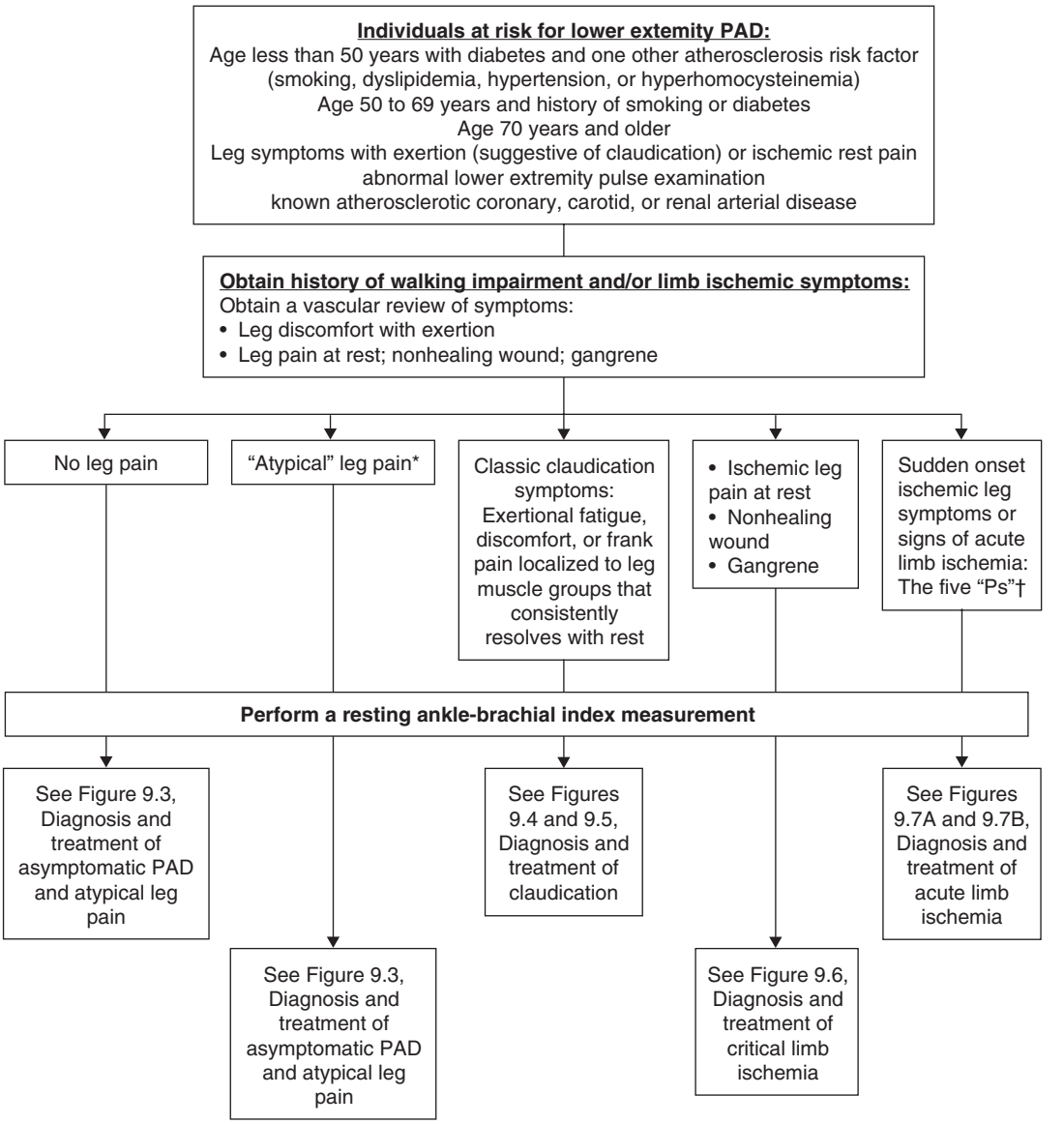


Fig. 9.2 Steps toward the diagnosis of peripheral arterial disease (PAD).
*"Atypical" leg pain is defined by lower extremity discomfort that is exertional, but that does not consistently resolve with rest, consistently limit exercise at a reproducible distance, or meet all "Rose questionnaire" criteria. †The five "Ps" are defined by the clinical symptoms and signs that suggest potential limb jeopardy: pain, pulselessness, pallor, paresthesias, and paralysis (with polar being a sixth "P").

rehabilitation) so as to determine functional capacity, assess nonvascular exercise limitations, and demonstrate the safety of exercise. *(Level of Evidence: B)*

Class IIb

A 6-minute walk test may be reasonable to provide an objective assessment of the functional limitation of claudication and response to therapy in elderly individuals or others not amenable to treadmill testing. *(Level of Evidence: B)*

Duplex ultrasound

Class I

1 Duplex ultrasound of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD. *(Level of Evidence: A)*

2 Duplex ultrasound is recommended for routine surveillance after femoral-popliteal or femoral-tibial pedal bypass with a venous conduit. Minimum surveillance intervals are approximately 3, 6, and 12 months, and then yearly after graft placement. *(Level of Evidence: A)*

Class IIa

1 Duplex ultrasound of the extremities can be useful to select patients as candidates for endovascular intervention. *(Level of Evidence: B)*

2 Duplex ultrasound can be useful to select patients as candidates for surgical bypass and to select the sites of surgical anastomosis. *(Level of Evidence: B)*

Class IIb

1 The use of duplex ultrasound is not well-established to assess long-term patency of percutaneous transluminal angioplasty. *(Level of Evidence: B)*

2 Duplex ultrasound may be considered for routine surveillance after femoral-popliteal bypass with a synthetic conduit. *(Level of Evidence: B)*

Computed tomographic angiography

Class IIb

1 Computed tomographic angiography of the extremities may be considered to diagnose anatomic location and presence of significant stenosis in patients with lower extremity PAD. *(Level of Evidence: B)*

2 Computed tomographic angiography of the extremities may be considered as a substitute for MRA for those patients with contraindications to MRA. *(Level of Evidence: B)*

Magnetic resonance angiography

Class I

1 Magnetic resonance angiography of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD. *(Level of Evidence: A)*

2 Magnetic resonance angiography of the extremities should be performed with gadolinium enhancement. *(Level of Evidence: B)*

3 Magnetic resonance angiography of the extremities is useful in selecting patients with lower extremity PAD as candidates for endovascular intervention. *(Level of Evidence: A)*

Class IIb

1 Magnetic resonance angiography of the extremities may be considered to select patients with lower extremity PAD as candidates for surgical bypass and to select the sites of surgical anastomosis. *(Level of Evidence: B)*

2 Magnetic resonance angiography of the extremities may be considered for post-revascularization (endovascular and surgical bypass) surveillance in patients with lower extremity PAD. *(Level of Evidence: B)*

Contrast angiography

Class I

1 Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated. *(Level of Evidence: B)*

2 A history of contrast reaction should be documented before the performance of contrast angiography and appropriate pretreatment administered before contrast is given. *(Level of Evidence: B)*

3 Decisions regarding the potential utility of invasive therapeutic interventions (percutaneous or surgical) in patients with lower extremity PAD should be made with a complete anatomic assessment of the affected arterial territory, including imaging of the occlusive lesion, as well as arterial inflow and outflow with angiography or a combination of angiography and noninvasive vascular techniques. *(Level of Evidence: B)*

4 Digital subtraction angiography is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography. *(Level of Evidence: A)*

5 Before performance of contrast angiography, a full history and complete vascular examination should be performed to optimize decisions regarding the access site, as well as to minimize contrast dose and catheter manipulation. *(Level of Evidence: C)*

6 Selective or superselective catheter placement during lower extremity angiography is indicated because this can enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure. *(Level of Evidence: C)*

7 The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap. *(Level of Evidence: B)*

8 When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, trans-stenotic pressure gradients and supplementary angulated views should be obtained. *(Level of Evidence: B)*

9 Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography. *(Level of Evidence: B)*

10 Follow-up clinical evaluation, including a physical examination and measurement of renal function, is recommended within 2 weeks after contrast angiography to detect the presence of delayed adverse effects such as atheroembolism, deterioration in renal function, or access site injury (e.g., pseudoaneurysm or arteriovenous fistula). *(Level of Evidence: C)*

Class IIa

1 Noninvasive imaging modalities, including MRA, CTA, and color flow duplex imaging, may be used in advance of invasive imaging to develop an individualized diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation. *(Level of Evidence: B)*

2 Treatment with *n*-acetylcysteine in advance of contrast angiography is suggested for patients with baseline renal insufficiency (creatinine greater than 2.0 mg per dl). *(Level of Evidence: B)*

Treatment

See Fig. 9.3.

All individuals with lower extremity PAD, whether asymptomatic or with limb symptoms, require medical treatment to reduce adverse cardiovascular event rates. Such lifelong treatment should include modification or elimination of atherosclerotic risk factors, such as cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension, and promotion of daily exercise and use of a nonatherogenic diet.

Cardiovascular risk reduction

Lipid-lowering drugs

Class I

Treatment with a hydroxymethyl glutaryl coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD to achieve a target low-density lipoprotein (LDL) cholesterol level of less than 100 mg per dl. *(Level of Evidence: B)*

Class IIa

1 Treatment with a hydroxymethyl glutaryl coenzyme-A reductase inhibitor (statin) medication to achieve a target LDL cholesterol level of less than 70 mg per dl is reasonable for patients with lower extremity PAD at very high risk of ischemic events. *(Level of Evidence: B)*

2 Treatment with a fibric acid derivative can be useful for patients with PAD and low high-density lipoprotein (HDL) cholesterol, normal LDL cholesterol, and elevated triglycerides. *(Level of Evidence: C)*

Antihypertensive drugs

Class I

1 Antihypertensive therapy should be administered to hypertensive patients with lower extremity PAD to achieve a goal of less than 140 mm Hg systolic over 90 mm Hg diastolic (nondiabetics) or less than 130 mm Hg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death. *(Level of Evidence: A)*

2 Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD. *(Level of Evidence: A)*

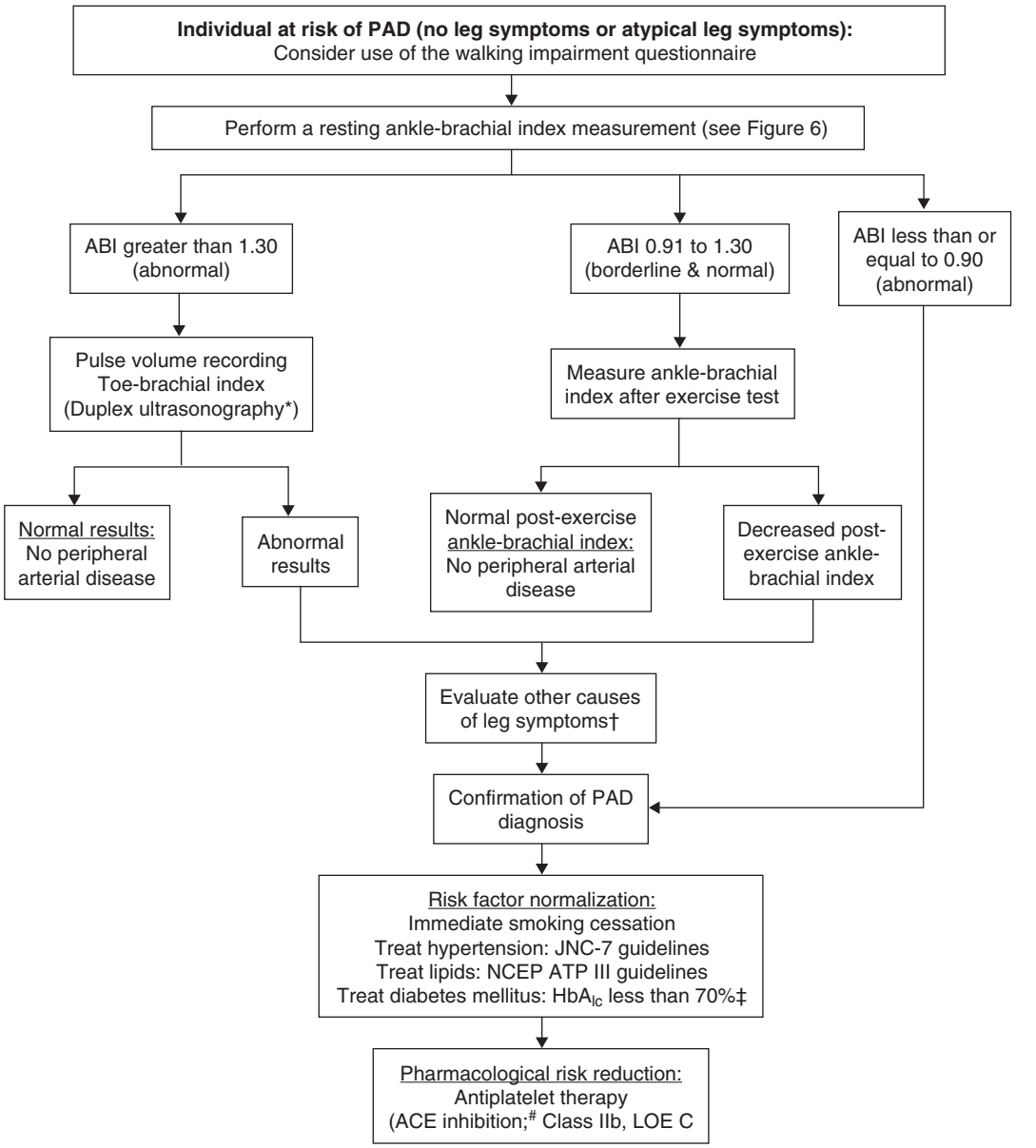


Fig. 9.3 Diagnosis and treatment of asymptomatic peripheral arterial disease (PAD) and atypical leg pain.

*Duplex ultrasonography should generally be reserved for use in symptomatic patients in whom anatomic diagnostic data is required for care.

†Other causes of leg pain may include: lumbar disk disease, sciatica, radiculopathy; muscle strain; neuropathy; compartment syndrome.

‡It is not yet proven that treatment of diabetes mellitus will significantly reduce PAD-specific (limb ischemic) endpoints. Primary treatment of diabetes mellitus should be continued according to established guidelines.

#The benefit of angiotensin-converting enzyme (ACE)-inhibition in individuals without claudication has not been specifically documented in prospective clinical trials, but has been extrapolated from other "at risk" populations.

ABI, ankle-brachial index; HgbA1c, hemoglobin A; JNC-7, Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LOE, level of evidence; NCEP ATP-III, National Cholesterol Education Program Adult Treatment Panel III.

Class IIa

The use of ACE inhibitors is reasonable for symptomatic patients with lower extremity PAD to reduce the risk of adverse cardiovascular events. *(Level of Evidence: B)*

Class IIb

Angiotensin-converting enzyme inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular events. *(Level of Evidence: C)*

Treatment of high blood pressure is indicated to reduce the risk of cardiovascular events. Beta-blockers, which have been shown to reduce the risk of MI and death in patients with coronary atherosclerosis, do not adversely affect walking capacity. Angiotensin-converting enzyme inhibitors reduce the risk of death and nonfatal cardiovascular events in patients with coronary artery disease and left ventricular dysfunction. The Heart Outcomes Prevention Evaluation (HOPE) trial found that in patients with symptomatic PAD, ramipril reduced the risk of MI, stroke, or vascular death by approximately 25%, a level of efficacy comparable to that achieved in the entire study population. There is currently no evidence base for the efficacy of ACE inhibitors in patients with asymptomatic PAD, and thus, the use of ACE-inhibitor medications to lower cardiovascular ischemic event rates in this population must be extrapolated from the data on symptomatic patients.

Diabetes therapies

Class I

Proper foot care, including use of appropriate footwear, chiropody/podiatric medicine, daily foot inspection, skin cleansing, and use of topical moisturizing creams should be encouraged, and skin lesions and ulcerations should be addressed urgently in all diabetic patients with lower extremity PAD. *(Level of Evidence: B)*

Class IIa

Treatment of diabetes in individuals with lower extremity PAD by administration of glucose control therapies to reduce the hemoglobin A1C to less than 7% can be effective to reduce microvascular complications and potentially improve cardiovascular outcomes. *(Level of Evidence: C)*

Smoking cessation

Class I

Individuals with lower extremity PAD who smoke cigarettes or use other forms of tobacco should be advised by each of their clinicians to stop smoking and should be offered comprehensive smoking cessation interventions, including behavior modification therapy, nicotine replacement therapy, or bupropion. *(Level of Evidence: B)*

Antiplatelet and antithrombotic drugs

Class I

1 Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: A)*

2 Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: A)*

3 Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: B)*

Class III

Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: C)*

Claudication

See Figs 9.4 and 9.5.

Claudication markedly limits functional status and impedes quality of life. There are now many proven therapies that can diminish claudication symptoms and there are no comparative data that demonstrate superiority of any single therapeutic approach. The roles of supervised exercise training and use of pharmacological treatment were emphasized as being effective, safe, and cost-effective, and therefore were emplaced as primary treatment strategies, not merely as "fall back options" if angioplasty could not be performed.

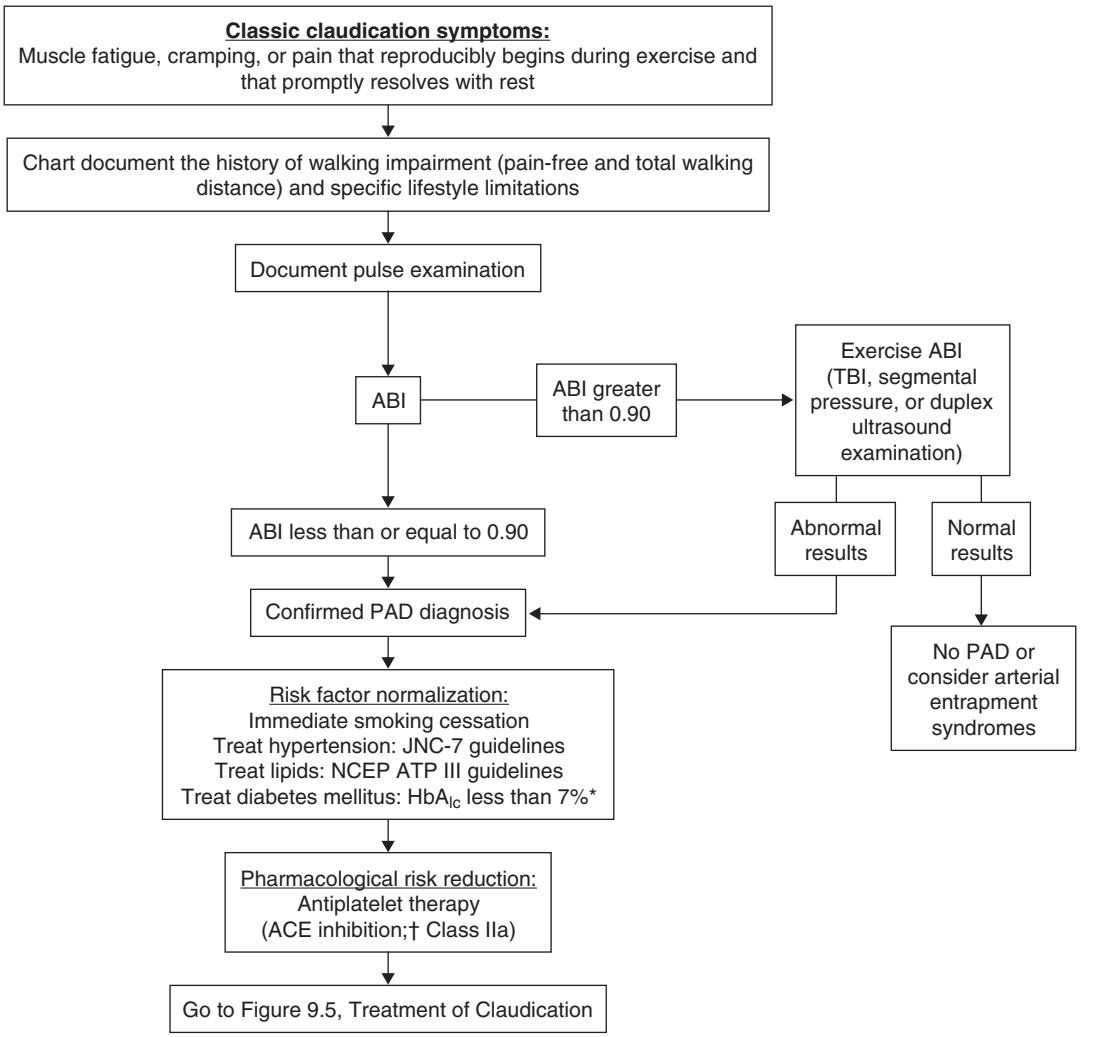


Fig. 9.4 Diagnosis of claudication and systemic risk treatment.

*It is not yet proven that treatment of diabetes mellitus will significantly reduce peripheral arterial disease (PAD)-specific (limb ischemic) endpoints. Primary treatment of diabetes mellitus should be continued according to established guidelines.

† The benefit of angiotensin-converting enzyme (ACE)-inhibition in individuals without claudication has not been specifically documented in prospective clinical trials, but has been extrapolated from other "at risk" populations.

ABI, ankle-brachial index; HgbA1c, hemoglobin A; JNC-7, Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LOE, level of evidence; NCEP ATP-III, National Cholesterol Education Program Adult Treatment Panel III.

Exercise and lower extremity pad rehabilitation

See Table 9.7.

Class I

1 A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. *(Level of Evidence: A)*

2 Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times per week for a minimum of 12 weeks. *(Level of Evidence: A)*

Class IIb

The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. *(Level of Evidence: B)*

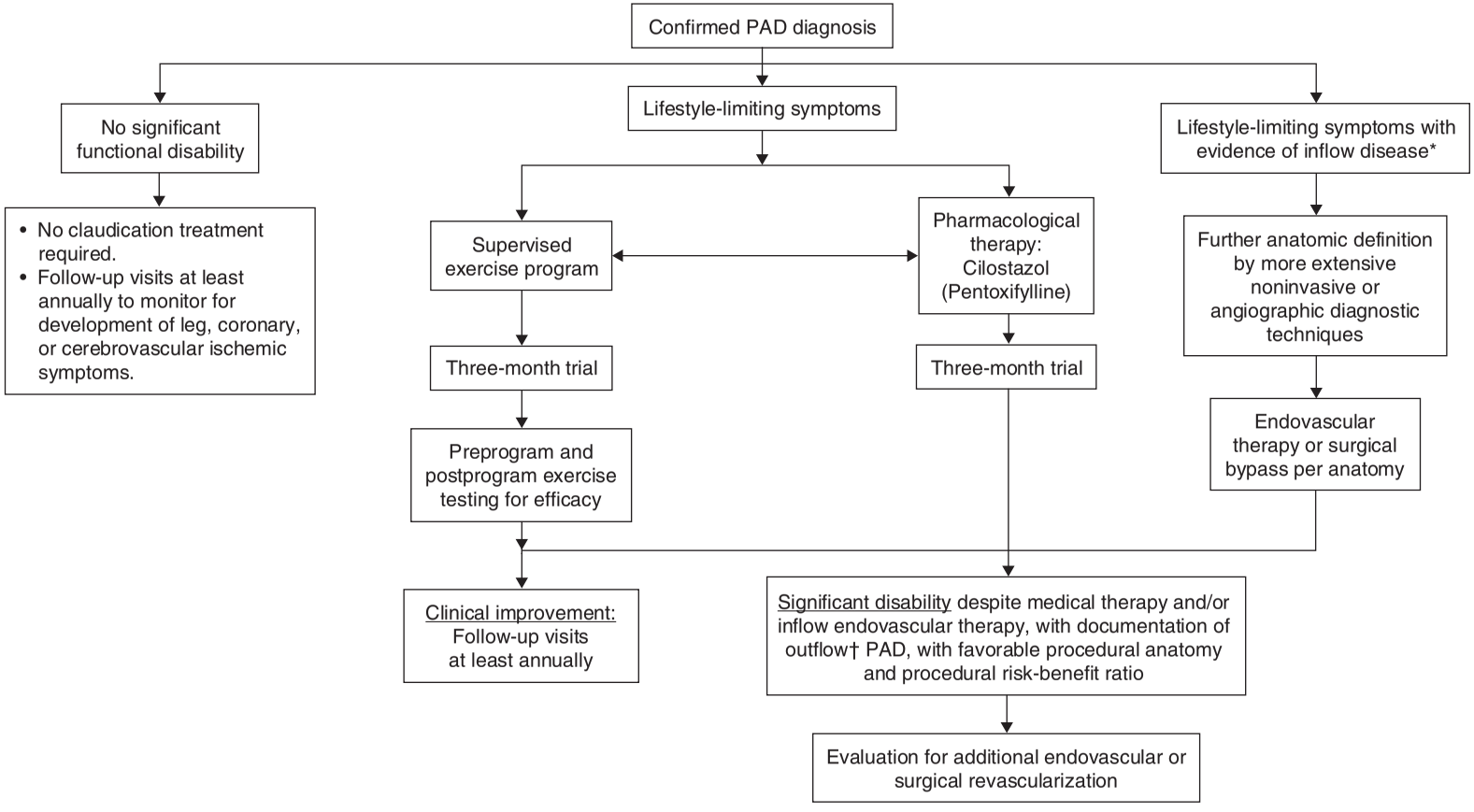


Fig. 9.5 Treatment of claudication.

*Inflow disease should be suspected in individuals with gluteal or thigh claudication and femoral pulse diminution or bruit and should be confirmed by noninvasive vascular laboratory diagnostic evidence of aortoiliac stenosis.

†Outflow disease represents femoropopliteal and infrapopliteal stenoses (the presence of occlusive lesions in the lower extremity arterial tree below the inguinal ligament from the common femoral artery to the pedal vessels).

Table 9.7 Key elements of a therapeutic claudication exercise training program (lower extremity PAD rehabilitation)

Primary clinician role
- Establish the PAD diagnosis using the ankle-brachial index measurement or other objective vascular laboratory evaluations
- Determine that claudication is the major symptom limiting exercise
- Discuss risk-benefit of claudication therapeutic alternatives including pharmacological, percutaneous, and surgical interventions
- Initiate systemic atherosclerosis risk modification
- Perform treadmill stress testing
- Provide formal referral to a claudication exercise rehabilitation program

Exercise guidelines for claudication*
- Warm-up and cool-down period of 5 to 10 minutes each

Types of exercise
- Treadmill and track walking are the most effective exercise for claudication.
- Resistance training has conferred benefit to individuals with other forms of cardiovascular disease, and its use, as tolerated, for general fitness is complementary to, but not a substitute for, walking.

Intensity
- The initial workload of the treadmill is set to a speed and grade that elicits claudication symptoms within 3 to 5 minutes
- Patients walk at this workload until they achieve claudication of moderate severity, which is then followed by a brief period of standing or sitting rest to permit symptoms to resolve

Duration
- The exercise-rest-exercise pattern should be repeated throughout the exercise session
- The initial duration will usually include 35 minutes of intermittent walking and should be increased by 5 minutes each session until 50 minutes of intermittent walking can be accomplished

Frequency
- Treadmill or track walking 3 to 5 times per week

Role of direct supervision
- As patients improve their walking ability, the exercise workload should be increased by modifying the treadmill grade or speed (or both) to ensure that there is always the stimulus of claudication pain during the workout
- As patients increase their walking ability, there is the possibility that cardiac signs and symptoms may appear (e.g., dysrhythmia, angina, or ST-segment depression). These events should prompt physician re-evaluation.

Pharmacological therapy of claudication

Class I

1 Cilostazol (100 mg orally twice a day) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). *(Level of Evidence: A)*

2 A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). *(Level of Evidence: A)*

Class IIb

1 Pentoxifylline (400 mg three times per day) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. *(Level of Evidence: A)*

2 The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well-established. *(Level of Evidence: C)*

Endovascular treatment for claudication

Because of the variability of individual limb ischemic symptoms and variable impact of these symp-

toms on quality of life, patients should be selected for revascularization on the basis of the severity of their symptoms; a significant disability as assessed by the patient; failure of medical therapies; lack of significant co-morbid conditions; vascular anatomy suitable for the planned revascularization; and a favorable risk/benefit ratio.

Class I

1 Endovascular procedures are indicated for individuals with a vocational or lifestyle-limiting disability due to intermittent claudication when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (a) there has been an inadequate response to exercise or pharmacological therapy and/or (b) there is a very favorable risk-benefit ratio (e.g., focal aortoiliac occlusive disease). *(Level of Evidence: A)*

2 Endovascular intervention is recommended as the preferred revascularization technique for Transatlantic Inter-Society Consensus type A iliac and femoropopliteal arterial lesions. *(Level of Evidence: B)*

3 Translesional pressure gradients (with and without vasodilation) should be obtained to evaluate the significance of angiographic iliac arterial stenoses of 50% to 75% diameter before intervention. *(Level of Evidence: C)*

4 Provisional stent placement is indicated for use in the iliac arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). *(Level of Evidence: B)*

5 Stenting is effective as primary therapy for common iliac artery stenosis and occlusions. *(Level of Evidence: B)*

6 Stenting is effective as primary therapy in external iliac artery stenoses and occlusions. *(Level of Evidence: C)*

Class IIa

Stents (and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices) can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection). *(Level of Evidence: C)*

Class IIb

1 The effectiveness of stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of femoral-popliteal arterial lesions (except to salvage a suboptimal result from balloon dilation) is not well established. *(Level of Evidence: A)*

2 The effectiveness of uncoated/uncovered stents, atherectomy, cutting balloons, thermal devices, and lasers for the treatment of infrapopliteal lesions (except to salvage a suboptimal result from balloon dilation) is not well established. *(Level of Evidence: C)*

Class III

1 Endovascular intervention is not indicated if there is no significant pressure gradient across a stenosis despite flow augmentation with vasodilators. *(Level of Evidence: C)*

2 Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries. *(Level of Evidence: C)*

3 Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD. *(Level of Evidence: C)*

Surgery for claudication

See Table 9.8.

Claudication rarely worsens to limb-threatening ischemia, and therefore neither patients nor clinicians should seek revascularization in order to avoid amputation and surgical treatment need not be a first line therapy. Operative intervention is usually utilized to treat the individual with claudication only after atherosclerosis risk factors have been

Table 9.8 Vascular surgical procedures for inflow improvement

Inflow procedure	Operative mortality (%)	Expected patency rates (%)
Aortobifemoral bypass	3.3	87.5 (5 yrs)
Aortoiliac or aortofemoral bypass	1–2	85–90 (5 yrs)
Iliac endarterectomy	0	79–90 (5 yrs)
Femorofemoral bypass	6	71 (5 yrs)
Axillofemoral bypass	6	49–80 (3 yrs)
Axillofemoral-femoral bypass	4.9	63–67.3 (5 yrs)

treated and an appropriate trial of exercise and/or claudication pharmacotherapy has been utilized. Intermittent claudication is considered a relative indication for surgical treatment and is usually reserved for individuals: (a) who do not derive adequate functional benefit from nonsurgical therapies; (b) who have limb arterial anatomy that is favorable to obtaining a durable clinical result; and (c) in whom the cardiovascular risk of surgical revascularization is low.

Indications

Class I

Surgical interventions are indicated for individuals with claudication symptoms who have a significant functional disability that is vocational or lifestyle limiting, who are unresponsive to exercise or pharmacotherapy, and who have a reasonable likelihood of symptomatic improvement. *(Level of Evidence: B)*

Class IIb

Because the presence of more aggressive atherosclerotic occlusive disease is associated with less durable results in patients younger than 50 years of age, the effectiveness of surgical intervention in this population for intermittent claudication is unclear. *(Level of Evidence: B)*

Class III

Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with intermittent claudication. *(Level of Evidence: B)*

Inflow procedures: aortoiliac occlusive disease

Class I

1 Aortobifemoral bypass is beneficial for patients with vocational- or lifestyle-disabling symptoms and hemodynamically significant aortoiliac disease who are acceptable surgical candidates and who are unresponsive to or unsuitable for exercise, pharmacotherapy, or endovascular repair. *(Level of Evidence: B)*

2 Iliac endarterectomy and aortoiliac or iliofemoral bypass in the setting of acceptable aortic inflow should be used for the surgical treatment of unilateral disease or in conjunction with femoral-femoral bypass for the treatment of a patient with bilateral iliac artery occlusive disease if the patient is not a suitable candidate for aortobifemoral bypass grafting. *(Level of Evidence: B)*

Class IIb

Axillofemoral-femoral bypass may be considered for the surgical treatment of patients with intermittent claudication in very limited settings, such as chronic infrarenal aortic occlusion associated with symptoms of severe claudication in patients who are not candidates for aortobifemoral bypass. *(Level of Evidence: B)*

Class III

Axillofemoral-femoral bypass should not be used for the surgical treatment of patients with intermittent claudication except in very limited settings (see Class IIb recommendation above). *(Level of Evidence: B)*

Outflow procedures: infrainguinal disease

Class I

1 Bypasses to the popliteal artery above the knee should be constructed with autogenous vein when possible. *(Level of Evidence: A)*

2 Bypasses to the popliteal artery below the knee should be constructed with autogenous vein when possible. *(Level of Evidence: B)*

Class IIa

The use of synthetic grafts to the popliteal artery below the knee is reasonable only when no autogenous vein from ipsilateral or contralateral legs or arms is available. *(Level of Evidence: A)*

Class IIb

1 Femoral-tibial artery bypasses constructed with autogenous vein may be considered for the treatment of claudication in rare instances for certain patients. *(Level of Evidence: B)*

2 Because their use is associated with reduced patency rates, the effectiveness of the use of synthetic grafts to the popliteal artery above the knee is not well established. *(Level of Evidence: B)*

Class III

Femoral-tibial artery bypasses with synthetic graft material should not be used for the treatment of claudication. *(Level of Evidence: C)*

Follow-up after vascular surgical procedures

Individuals who have undergone vascular surgical procedures require ongoing care, inclusive of achievement of risk reduction goals and often surveillance of the operative bypass if the most durable graft patency is to be achieved.

Class I

1 Patients who have undergone placement of aortobifemoral bypass grafts should be followed up with periodic evaluations that record any return or progression of claudication symptoms, the presence of femoral pulses, and ABIs at rest and after exercise. *(Level of Evidence: C)*

2 Patients who have undergone placement of a lower extremity bypass with autogenous vein should undergo periodic evaluations for at least 2 years that record any claudication symptoms; a physical examination and pulse examination of the proximal, graft, and outflow vessels; and duplex imaging of the entire length of the graft, with measurement of peak systolic velocities and calculation of velocity ratios across all lesions. *(Level of Evidence: C)*

3 Patients who have undergone placement of a synthetic lower extremity bypass graft should, for at least 2 years after implantation, undergo periodic evaluations that record any return or progression of claudication symptoms; a pulse examination of the proximal, graft, and outflow vessels; and assessment of ABIs at rest and after exercise. *(Level of Evidence: C)*

Critical limb ischemia and treatment for limb salvage

See Figs 9.6, 9.7A and 9.7B.

Chronic critical limb ischemia is associated with a 1-year mortality rate greater than 20%. Nearly half of the cases will require revascularization for limb salvage. Among those who have unreconstructable disease, approximately 40% will require major amputation within 6 months of initial diagnosis. This natural history mandates a more aggressive approach to control of atherosclerosis risk factors and treatment of underlying ischemia on the part of physicians caring for this critically ill group of patients.

Medical and pharmacological treatment for CLI

Class IIb

Parenteral administration of prostaglandin E-1 (PGE-1) or iloprost for 7 to 28 days may be considered to reduce ischemic pain and facilitate ulcer healing in patients with CLI, but its efficacy is likely to be limited to a small percentage of patients. *(Level of Evidence: A)*

Class III

Parenteral administration of pentoxifylline is not useful for the treatment of CLI. *(Level of Evidence: B)*

Thrombolysis for acute and chronic limb ischemia

Class I

Catheter-based thrombolysis is an effective and beneficial therapy and is indicated for patients with acute limb ischemia (Rutherford categories I and IIa) of less than 14 days' duration. *(Level of Evidence: A)*

Class IIa

Mechanical thrombectomy devices can be used as adjunctive therapy for acute limb ischemia due to peripheral arterial occlusion. *(Level of Evidence: B)*

Class IIb

Catheter-based thrombolysis or thrombectomy may be considered for patients with acute limb ischemia (Rutherford category IIb) of more than 14 days' duration. *(Level of Evidence: B)*

Surgery for CLI

Class I

1 For individuals with combined inflow and outflow disease with CLI, inflow lesions should be addressed first. *(Level of Evidence: B)*

2 For individuals with combined inflow and outflow disease in whom symptoms of CLI or infection persist after inflow revascularization, an outflow revascularization procedure should be performed. *(Level of Evidence: B)*

3 Patients who have significant necrosis of the weightbearing portions of the foot (in ambulatory patients), an uncorrectable flexion contracture, paresis of the extremity, refractory ischemic rest pain, sepsis, or a very limited life expectancy due to comorbid conditions should be evaluated for primary amputation of the leg. *(Level of Evidence: C)*

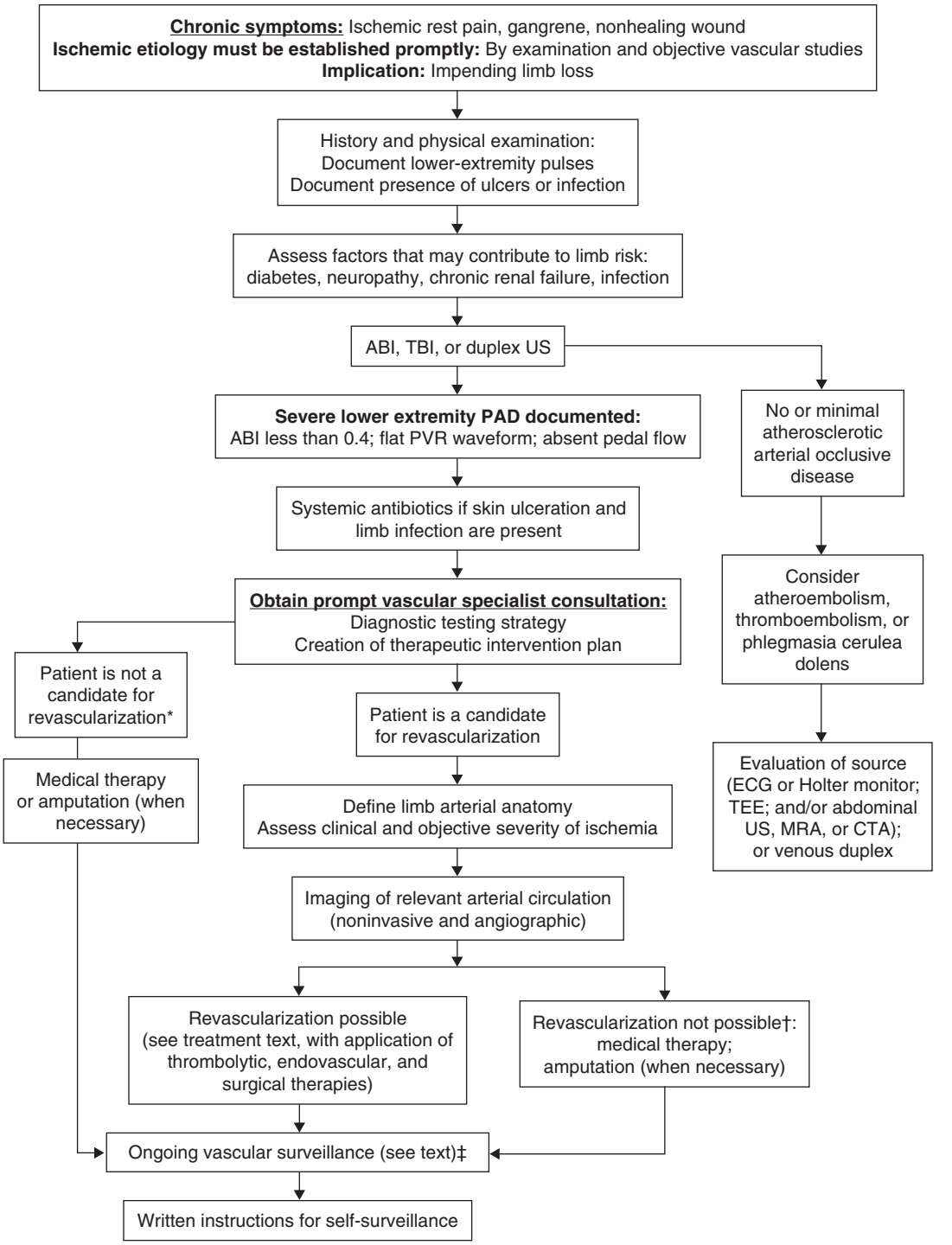


Fig. 9.6 Diagnosis and treatment of critical limb ischemia (CLI).

*Based on patient comorbidities.

†Based on anatomy or lack of conduit.

‡Risk factor normalization: immediate smoking cessation, treat hypertension per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines; treat lipids per National Cholesterol Education Program Adult Treatment Panel III guidelines; treat diabetes mellitus (HgbA1c [hemoglobin A] less than 7%; Class IIa). It is not yet proven that treatment of diabetes mellitus will significantly reduce peripheral arterial disease (PAD)-specific (limb ischemic) endpoints. Primary treatment of diabetes mellitus should be continued according to established guidelines.

ABI, ankle-brachial index; CTA, computed tomographic angiography; ECG, electrocardiogram; MRA, magnetic resonance angiography; PVR, pulse volume recording; TBI, toe-brachial index; TEE, transesophageal echocardiography; US, ultrasound.

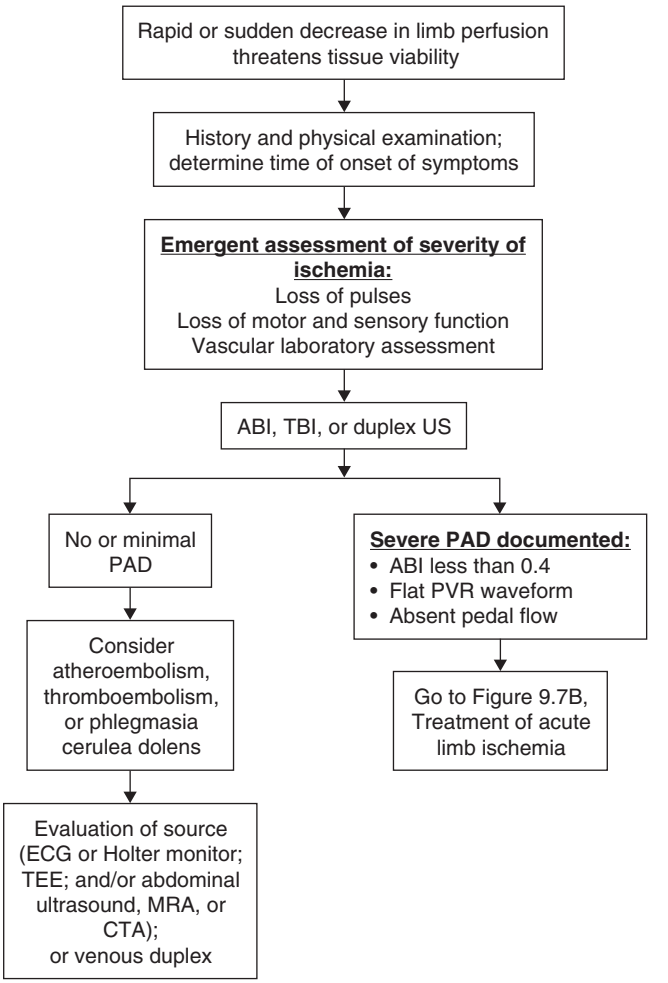


Fig. 9.7 A, Diagnosis of acute limb ischemia. Adapted from J Vasc Surg 26, Rutherford RB, Baker JD, Ernst C, *et al.*, Recommended standards for reports dealing with lower extremity ischemia: revised version, 517–38, Copyright 1997, with permission from Elsevier.
ABI, ankle-brachial index; CTA, computed tomographic angiography; ECG, electrocardiogram; MRA, magnetic resonance angiography; PVR, pulse volume recording; TBI, toe-brachial index; TEE, Transesophageal echocardiography.

Class III

Surgical and endovascular intervention is not indicated in patients with severe decrements in limb perfusion (e.g., ABI less than 0.4) in the absence of clinical symptoms of CLI. *(Level of Evidence: C)*

Inflow procedures: aortoiliac occlusive disease

Class I

1 When surgery is to be undertaken, aortobifemoral bypass is recommended for patients with symptomatic, hemodynamically significant, aorto-bi-iliac disease requiring intervention. *(Level of Evidence: A)*

2 Iliac endarterectomy, patch angioplasty, or aortoiliac or iliofemoral bypass in the setting of acceptable aortic inflow should be used for the treatment of unilateral disease or in conjunction with femoral-femoral bypass for the treatment of a patient with bilateral iliac artery occlusive disease if the patient is not a suitable candidate for aortobifemoral bypass grafting. *(Level of Evidence: B)*

3 Axillofemoral-femoral bypass is indicated for the treatment of patients with CLI who have extensive aortoiliac disease and are not candidates for other types of intervention. *(Level of Evidence: B)*

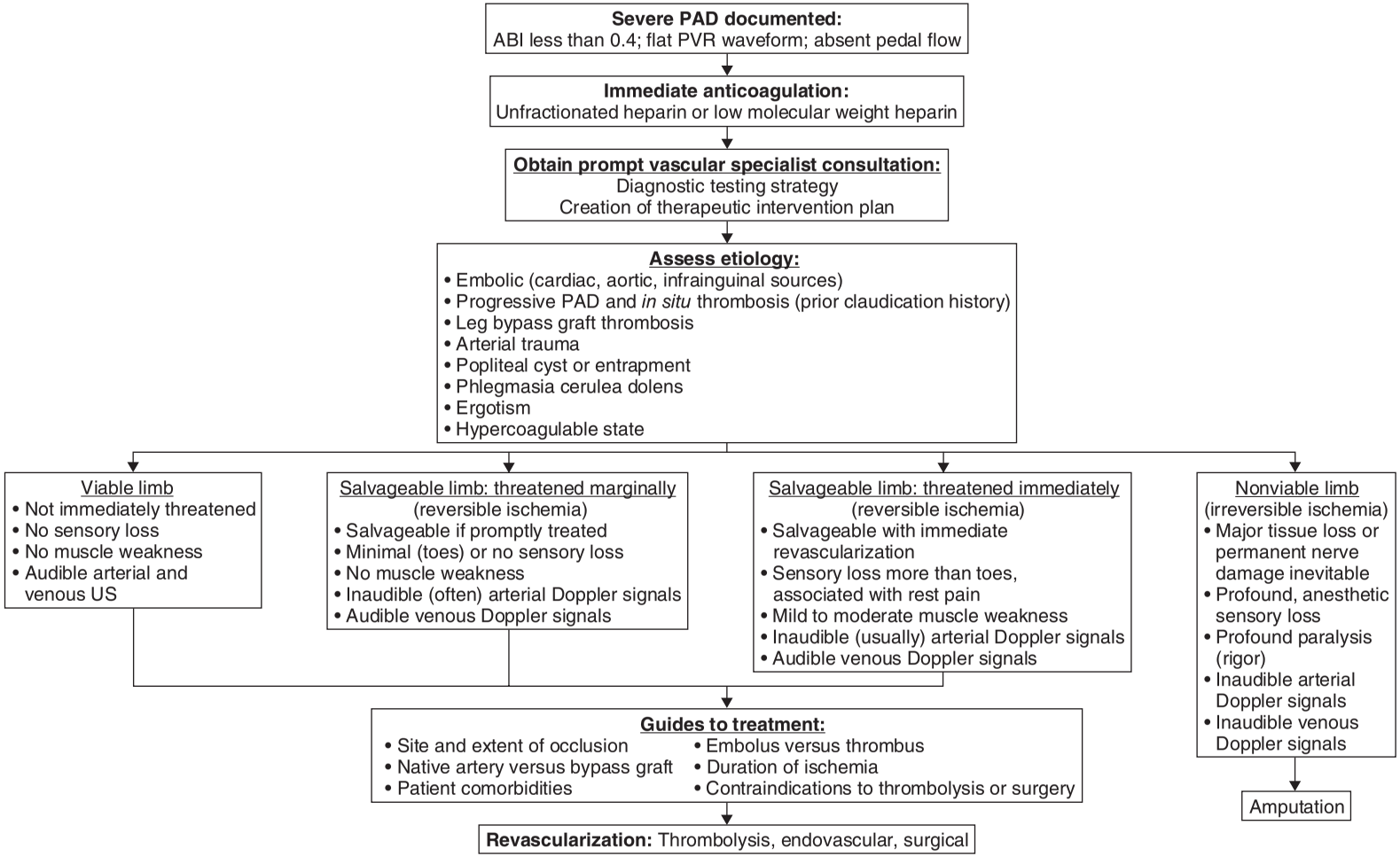


Fig. 9.7 B, Treatment of acute limb ischemia. Adapted from J Vasc Surg, Rutherford RB, Baker JD, Ernst C, *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version, 517–38, Copyright 1997, with permission from Elsevier.

PAD, peripheral arterial disease; PVR, pulse volume recording; US, ultrasound.

Outflow procedures: infrainguinal disease

Class I

1 Bypasses to the above-knee popliteal artery should be constructed with autogenous saphenous vein when possible. *(Level of Evidence: A)*

2 Bypasses to the below-knee popliteal artery should be constructed with autogenous vein when possible. *(Level of Evidence: A)*

3 The most distal artery with continuous flow from above and without a stenosis greater than 20% should be used as the point of origin for a distal bypass. *(Level of Evidence: B)*

4 The tibial or pedal artery that is capable of providing continuous and uncompromised outflow to the foot should be used as the site of distal anastomosis. *(Level of Evidence: B)*

5 Femoral-tibial artery bypasses should be constructed with autogenous vein, including the ipsilateral greater saphenous vein, or if unavailable, other sources of vein from the leg or arm. *(Level of Evidence: B)*

6 Composite sequential femoropopliteal-tibial bypass and bypass to an isolated popliteal arterial segment that has collateral outflow to the foot are both acceptable methods of revascularization and should be considered when no other form of bypass with adequate autogenous conduit is possible. *(Level of Evidence: B)*

7 If no autogenous vein is available, a prosthetic femoral-tibial bypass, and possibly an adjunctive procedure, such as arteriovenous fistula or vein interposition or cuff, should be used when amputation is imminent. *(Level of Evidence: B)*

Class IIa

Prosthetic material can be used effectively for bypasses to the below-knee popliteal artery when no autogenous vein from ipsilateral or contralateral leg or arms is available. *(Level of Evidence: B)*

Postsurgical care

Class I

1 Unless contraindicated, all patients undergoing revascularization for CLI should be placed on antiplatelet therapy, and this treatment should be continued indefinitely. *(Level of Evidence: A)*

2 Patients who have undergone placement of aortobifemoral bypass grafts should be followed up with periodic evaluations that record any return or progression of ischemic symptoms, the presence of femoral pulses, and ABIs. *(Level of Evidence: B)*

3 If infection, ischemic ulcers, or gangrenous lesions persist and the ABI is less than 0.8 after correction of inflow, an outflow procedure should be performed that bypasses all major distal stenoses and occlusions. *(Level of Evidence: A)*

4 Patients who have undergone placement of a lower extremity bypass with autogenous vein should undergo for at least 2 years periodic examinations that record any return or progression of ischemic symptoms; a physical examination, with concentration on pulse examination of the proximal, graft, and outflow vessels; and duplex imaging of the entire length of the graft, with measurement of peak systolic velocities and calculation of velocity ratios across all lesions. *(Level of Evidence: A)*

5 Patients who have undergone placement of a synthetic lower extremity bypass graft should undergo periodic examinations that record any return of ischemic symptoms; a pulse examination of the proximal, graft, and outflow vessels; and assessment of ABIs at rest and after exercise for at least 2 years after implantation. *(Level of Evidence: A)*

Other guidelines: The Trans-Atlantic Inter-Society Consensus Documents, TASC-I and TASC-II

In 2000, the first Trans-Atlantic Inter-Society Consensus Document on the Management of Peripheral Arterial Disease (TASC) was published [4], and the original document was updated in 2006 [5]. This document was the collaborative product of 14 vascular surgery, vascular medicine, cardiology, and interventional radiology societies from North America and Europe. The original document differed from the AHA/ACC PAD Guideline in that the focus was directed more toward vascular specialists. For example, grading systems for describing lesion location and characteristics were created, followed by recommended medical, endovascular, and surgical approaches for use of each therapy.

In 2004, the TASC group began its second consensus process, broadening its scope in the revised TASC-II guideline [5] by including recommendations intended for use by the vascular specialist, as well as by a broader audience of all physicians who might treat lower extremity PAD. In a manner

similar to the AHA/ACC guideline approach, TASC recommendations are assigned a level of evidence, though the grading system is different. TASC-II recommendations are denoted as A, B, and C. Grade A recommendations are based upon "at least one randomized, controlled clinical trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation." Grade B recommendations are based upon "well-conducted clinical studies [in the absence of] good quality randomized clinical trials." Grade C recommendations are based upon "evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities."

Since TASC-II recommendations are based upon much of the same literature that was available at the time of preparation of the ACC/AHA PAD Guideline, there is broad consensus between both documents, such as specific recommendations in the areas of cardiovascular risk factor reduction, use of pharmacotherapies and exercise, assessment of coexistent atherosclerotic disease in other arterial beds, such as the cardiac or cerebrovascular systems, and appropriate use of diagnostic imaging and physiologic studies (e.g., primary use of the ABI test to diagnose lower extremity PAD). The differences are most notable in areas written specifically for the practicing vascular specialist. TASC-II provides detailed recommendations for the indications, merits, and performance of endovascular and surgical therapies for lower extremity arterial disease. For example, recommendations range from indications and contraindications for catheter-directed thrombolysis, performance of completion arteriography after surgical arterial embolectomy, and use of anatomic-based recommendations for angioplasty and stent use in the infrainguinal circulation (based upon the TASC classification of lesion anatomy). Finally, unlike the ACC/AHA Guideline, the TASC Guideline focus is primarily upon occlusive disease and generally does not address management of individuals with abdominal aortic or peripheral arterial aneurysms (except for lower extremity thromboses that manifest as limb ischemia due to popliteal artery aneurysms).

Ongoing trials and future directions on PAD care

As for other cardiovascular care fields, evidence-based recommendations are created from pro-spectively designed clinical trials, supported by epidemiologic surveys, case series, and expert opinion. Since original Guideline publication in 2006, selected new studies have become available or are in progress. This chapter is not designed to review such studies nor to alter care recommendations emplaced in a peer-reviewed, intersocietal guideline. However, studies that may merit review upon guideline update may include the BASIL study of revascularization strategies for critical limb ischemia, which has demonstrated parity of endovascular care to open surgical revascularization for individuals with critical limb ischemia [6]; the ABSOLUTE trial, which has demonstrated short-term benefit from primary stenting of the superficial femoral artery compared with balloon angioplasty alone, though evidence for longer term (multiyear) benefit remains lacking [7]; and the NHLBI-sponsored Claudication: Exercise vs. Endoluminal Revascularization (CLEVER), which has offered a PAD trial design template that should provide comparative efficacy and safety data from a "strategy of care" perspective [8].

New insights regarding the risk of lower extremity PAD conferred by ethnicity have been demonstrated in the NHLBI-sponsored Multi-Ethnic Studies of Atherosclerosis (MESA) study [9]. Major new insights confirming the superiority of antiplatelet therapy vs. warfarin has been provided from the WAVE trial of warfarin vs. aspirin in prevention of ischemic events in individuals with PAD, demonstrating the superiority of antiplatelet medications [10].

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

10 Cholesterol Management in the Context of Risk Factor Profile

Scott M. Grundy

Sources
LDL Cholesterol: the primary target of therapy
Risk assessment: first step in risk management
Goals for cholesterol lowering therapy
Role of other risk factors in risk assessment
Secondary causes of lipid disorders
Therapeutic approaches to cholesterol-lowering therapy
Therapeutic lifestyle changes
Drug therapy
Adherence to LDL-lowering therapy
Special and unresolved issues
Management of specific dyslipidemias
Very high LDL cholesterol (≥190 mg/dL)
Elevated serum triglycerides
Low HDL-C
Metabolic syndrome
Other unresolved issues
European guidelines for lipid management

Sources

The information contained in this chapter synthesizes the evidence presented in the 2001 National Cholesterol Education Program's (NCEP's) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) [1], the 2004 update of the ATP III report [2], and 2007 American Heart Association Secondary Prevention Guidelines [3].

It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

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LDL Cholesterol: the primary target of therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol (LDL-C) is a major cause of coronary heart disease (CHD) and cardiovascular disease (CVD). In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. Although ATP III [1] identified prevention of CHD as the major aim of cholesterol-lowering therapy, in the light of recent clinical trials, there is a trend to expand the endpoint to include all of atherosclerotic CVD [4].

Based results of multiple lines of evidence, LDL-C constitutes the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL-C [1–3]. Clinical trial evidence that LDL-lowering significantly reduces risk for CVD is very strong (summarized in refs 1–3). *(Level of Evidence: A)*

Growing evidence indicates that very low density lipoprotein (VLDL) approaches LDL in atherogenic potential. Thus, in patients with higher triglyceride, the sum of LDL + VLDL cholesterol (usually called non-HDL-C) is a better predictor of atherosclerotic risk than is LDL-C alone. Although some investigators contend that non-HDL-C is a preferred primary target of therapy over LDL-C [5–7], this view has not been universally accepted. For this reason, non-HDL-C is designated a secondary target of choles-

Table 10.1 Classification of lipoprotein cholesterol levels

LDL cholesterol	
<100	Optimal
100–129	Above optimal/near optimal
130–159	Borderline high
160–189	High
≥190	Very high
Non-HDL-Cholesterol	
<130	Optimal
130–159	Above optimal/near optimal
160–189	Borderline high
190–220	High
≥220	Very high
Total cholesterol	
<200	Desirable
200–239	Borderline-high
≥240	High
HDL cholesterol	
<40	Low
≥60	High

Table 10.2 Risk categories for coronary heart disease

Risk category
Very high risk Recent myocardial Infarction (acute coronary syndrome) or CHD[a] + CHD risk equivalents[b] (or + multiple risk factors[c] and/or metabolic syndrome[d])
High risk CHD or CHD risk equivalents (10-year risk for CHD >20%)
Moderately high risk 2+ risk factors (10-year risk for CHD 10–20%)
Moderate risk 2+ risk factors (10-year risk for CHD <10%)
Lower risk 0–1 risk factor

[a] CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or by-pass surgery), or evidence of clinically significant myocardial ischemia.

[b] CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD > 20%.

[c] Risk factors include cigarette smoking, hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years), and age (men ≥45 years; women ≥55 years).

[d] Metabolic syndrome is defined by 3 or more of the following risk factors: abdominal obesity (waist circumference ≥102 cm in men or ≥88 cm in women), elevated triglycerides (≥150 mg/dL), reduced HDL-C (<40 mg/dL in men or <50 mg/dL in women), elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic), plasma glucose ≥100 mg/dL, or on drug treatment for any of these conditions.

[e] Almost all people with 0–1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with 0–1 risk factor is thus not necessary.

terol-lowering-therapy, especially for persons with elevated triglycerides. *(Level of Evidence: B)*

Epidemiological evidence shows a strong inverse association between high density lipoprotein cholesterol (HDL-C) and CVD [1]. Whether a low HDL-C directly promotes atherosclerosis or is only a marker for other risk factors is uncertain. To date, only limited clinical trial evidence suggests that raising HDL-C may reduce risk for CVD [8]. *(Level of Evidence: C)*

NCEP guidelines provide a classification of total cholesterol, LDL-C, non-HDL-C, and HDL-C as a guide to therapeutic goals (Table 10.1).

Risk assessment: first step in risk management

The first step in selection of cholesterol-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL-C as part of lipoprotein analysis and identification of accompanying risk determinants. Risk categories are defined in Table 10.2. For patients without CVD or CHD risk equivalents (defined in Table 10.2) and when 2+ risk factors are present, risk assessment by Framingham risk scoring adds refinement to absolute risk assessment. It is preferable to do Framingham risk scoring electronically (see http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm [10-year risk calculator {on-line version}]).

Table 10.3 Categories of risk that modify LDL-cholesterol goals

Risk category	LDL goal (mg/dL)	Non-HDL-C Goal (mg/dL)
Very high risk	<70[a]	<100[a]
High risk	<100[b]	<130[a]
Moderately high risk	<130[c] (Optional <100[d])	<160[c] (Optional <130[d])
Moderate risk	<130[e]	<160[e]
Lower risk	<160[f]	<190[f]

[a] Level of Evidence B.
[b] Level of Evidence A.
[c] Level of Evidence A.
[d] Level of Evidnece B.
[e] Level of Evidence A.
[f] Level of Evidence B.

Goals for cholesterol lowering therapy

Goals of therapy follow the principle that the higher the risk of the patients, the more intensive should be the risk-reduction therapy. The updated goals for cholesterol-lowering therapy are shown in Table 10.3. Evidence level for each goal is given in the footnotes to Table 10.3.

Role of other risk factors in risk assessment

ATP III recognizes that risk for CHD, as well as CVD, is influenced by other factors not included among the major, independent risk factors (Table 10.4). Among these are *life-habit risk factors* and *emerging risk factors.* The former include obesity, physical inactivity, and atherogenic diet; and the latter consist of lipoprotein(a) [Lp(a)], homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The *life-habit risk factors* are direct targets for clinical intervention, but are not used to set a lower LDL-C goal of therapy. The *emerging risk factors* do not categorically modify LDL-C goals; however, they appear to contribute to CVD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence thus can modulate clinical judgment when making therapeutic decisions based physician discretion.

Table 10.4 Nutrient composition of the cholesterol-lowering diet

Nutrient	Recommended intake
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories
Carbohydrate[†]	50 to 60% of total calories
Fiber	20–30 grams per day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)[‡]	Balance energy intake and expenditure to maintain desirable body weight/ prevent weight gain

* Trans fatty acids are another LDL-raising fat that should be kept at a low intake.
[†] Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
[‡] Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

Secondary causes of lipid disorders

Any person with elevated LDL-C or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that raise LDL-C and lower HDL-C (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in prevention are established according to a person's risk category (Table 10.3).

Therapeutic approaches to cholesterol-lowering therapy

Cholesterol-management guidelines focus on goals of therapy [1–3]. The primary target of therapy is LDL-C. Non-HDL-C is a secondary target in patients with plasma triglycerides ≥200 mg/dL. However,

Table 10.5 Drugs affecting lipoprotein metabolism

Drug class, agents and daily doses	Lipid/lipoprotein effects	Side effects	Contraindications	Clinical trial results
HMG CoA reductase inhibitors (statins)*	LDL-C ↓ 18–55% HDL-C ↑ 5–15% TG ↓ 7–30%	Myopathy Increased liver enzymes	Absolute: • Active liver disease Relative: • Concomitant use of certain drugs‡ • Chronic liver disease (e.g. fatty liver, hepatitis C)	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants†	LDL-C ↓ 15–30% HDL-C ↑ 3–5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • Dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL	Reduced major coronary events and CHD deaths
Ezetimibe	LDL-C ↓ 15–25%	Few		Benefit not demonstrated with controlled trials
Nicotinic acid¥	LDL-C ↓ 5–25% HDL-C ↑ 15–35% TG ↓ 20–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes (requires close monitoring) • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL-C ↓ 5–20% (may be increased in patients with high TG) HDL-C ↑ 10–20% TG ↓ 20–50%	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic disease	Reduced major coronary events Suggestion of increased non-CHD mortality

* Lovastatin (20–80 mg), pravastatin (20–40 mg), simvastatin (20–80 mg), fluvastatin (20–80 mg), atorvastatin (10–80 mg), resuvastatin (5–40 mg).

† Cholestyramine (4–16 g), colestipol (5–20 g), colesevelam (2.6–3.8 g) Ezetimibe (10 mg).

‡ Cyclosporine, gemfibrozil (or niacin), macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors.

¥ Immediate release (crystalline) nicotinic acid (1.5–3 g), extended release nicotinic acid (Niaspan®) (1–2 g), sustained release nicotinic acid (1–2 g).

§ Gemfibrozil (600 mg BID), fenofibrate (48–200 mg), clofibrate (1000 mg BID).

some authorities routinely employ non-HDL-C as a secondary target in all patients. One advantage of non-HDL-C is that its measurement does not require a fasting state for accuracy. Two modalities of therapy can be employed to achieve the goals of cholesterol-lowering therapy. These are *therapeutic lifestyle changes (TLC)* and *drug therapy*. Lifestyle therapies should be employed in all patients. Drug therapy, however, is often required to achieve the goals of therapy, particularly in persons at higher risk.

Therapeutic lifestyle changes

ATP III [1] recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated *therapeutic lifestyle changes (TLC)*. Its essential features are:

• Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day) (see Table 10.4 for overall composition of the TLC diet)
• Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10–25 g/d)
• Weight reduction
• Increased physical activity.

Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative [9].

These guidelines are available on-line http://www.nhlbi.nih.gov/guidelines/obesity/index.htm). Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy,* which is the term for the intervention and guidance provided by a nutrition professional.

Drug therapy

A portion of the population whose short-term and/or long-term risks for CHD are high will require LDL-lowering drugs in addition to TLC to reach the prescribed goal for LDL-C. When drugs are employed, attention to TLC should always be maintained and reinforced. Currently available drugs affecting lipoprotein metabolism and their major characteristics are listed in Table 10.5.

Adherence to LDL-lowering therapy

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of CHD risk reduction. Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (Table 10.6).

Table 10.6 Interventions to improve adherence

Focus on the patient
- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help persons remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase patient visits for persons unable to achieve treatment goal
- Increase the convenience and access to care
- Involve persons in their care through self-monitoring

Focus on the physician and medical office
- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow-up missed appointments

Focus on the health delivery system
- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Special and unresolved issues

There is a host of questions related to cholesterol management for which controlled clinical trials have not been specifically carried out. On the basis of both epidemiology and clinical trials, it can be said that in general *the lower, the better* for both LDL-C and non-HDL-C [10,11].

With this principle in mind, clinical guidelines for cholesterol-lowering therapy have not differentiated among subgroups but have adopted the position that *the intensity of therapy should be proportional to the*

absolute risk of the patient. Guidelines are designed to provide an appropriate balance among efficacy, safety, and cost-effectiveness of therapies, but beyond this principle, efficacy for particular subgroups of the population is not questioned. Not all investigators are in agreement with this approach. Some would require that efficacy and safety be proved for every subgroup – men and women, younger and older, non-diabetic and diabetic, each ethnic groups, etc. – before recommendations can be extended to particular subgroups. This of course is an impossible demand because of high costs and lack of funding commitment. As a middle ground, clinical-management recommendations could be based on either smaller clinical trials, from subgroup analyses from larger trials, from epidemiological evidence, or from many years of clinical experience in the lipid field. This problem for specific recommendations goes beyond current guidelines for evidence-based medicine because no rules have ever been established for applying clinical-trial evidence to many different subgroups of the population. A reasonable compromise may be to reduce the Level of Evidence by one grade to an untested subgroup where evidence is firm in a mixed cohort of tested subjects. The following addresses some of the pressing questions about cholesterol management for which clinical-trial evidence is limited.

Management of specific dyslipidemias

Very high LDL cholesterol (≥190 mg/dL)

Persons with very high LDL-C usually have genetic forms of hypercholesterolemia, i.e., monogenic familial hypercholesterolemia, familial defective apolipoprotein B, or polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD [12]. When hypercholesterolemic individuals are identified, family testing is important to detect similarly affected relatives. These disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering treatment [1].

Elevated serum triglycerides

Elevated triglycerides have been identified as *independent risk factor* for CHD [13,14].

This finding supports the concept that VLDL is an atherogenic lipoprotein. Beyond an indication of elevated VLDL-C, high triglycerides raise the possibility of a variety of metabolic disorders or metabolic consequences of drug therapy. Examples include obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, type 2 diabetes, chronic renal failure, nephrotic syndrome, certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia). In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III [1] adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150–199 mg/dL
- High triglycerides: 200–499 mg/dL
- Very high triglycerides: ≥500 mg/dL

When triglycerides are in the range of 150 to 499 mg/dL, they are especially useful as an indicator of a metabolic disorder. For lipid-management purposes, triglycerides can be subsumed within non-HDL-C and do not require special clinical attention as a separate lipid target of therapy. When triglycerides are ≥500 mg/dL, they pose a potential risk for acute pancreatitis; the higher the triglycerides, the greater the risk. Most patients with a very high triglyceride will require therapy with a triglyceride-lowering drug (e.g., fibrate, nicotinic acid, or high doses of N-3 fatty acids). The goal is to reduce the level to <500 mg/dL, which will largely eliminate the risk for pancreatitis. Patients with very high triglycerides should be counseled to consume a very low-fat diet (<15% of calories as fat). In hypertriglyceridemic patients with diabetes, improvement of glycemic control will facilitate reduction of triglyceride levels, but an underlying genetic dyslipidemia is commonly present as well.

Low HDL-C

Low levels of HDL-C are strongly associated with risk for CHD [15]. ATP III guidelines, low HDL-C both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD. Low HDL-C levels have several causes, many of which are associated with insulin resistance, i.e., elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette

smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (e.g., beta-blockers, anabolic steroids, progestational agents). ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Further, currently available drugs do not robustly raise HDL-C. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL-C, the primary target of therapy is LDL-C and non-HDL-C a secondary goal. Since there are no drugs that specifically raise HDL-C independently of lowering apo B-containing lipoproteins, it has not been possible to test the hypothesis that HDL-raising therapy will reduce risk for CHD. Therefore, any therapeutic effort to raise HDL-C for the purpose of reducing CHD is based on speculation based on epidemiology, animal studies, and limited clinical studies.

Metabolic syndrome

The metabolic syndrome is a multiplex risk factor for CVD [16,17]. ATP III identified the metabolic syndrome as a risk partner with LDL-C because of its association with the increasing prevalence of obesity in the United States and worldwide. To a significant extent the metabolic syndrome represents the metabolic consequence of obesity, although other factors are involved in its pathogenesis. Not only is the syndrome a multilayered risk factor for CVD but it carries increased risk for type 2 diabetes and is associated with other conditions including nonalcoholic fatty liver disease, cholesterol gallstones, obstructive sleep apnea, and polycystic ovarian syndrome. The syndrome is most strongly associated with abdominal obesity but other factors – physical inactivity, insulin resistance, endocrine dysfunction, and racial/ethic predisposition – contribute to its development. The syndrome is characterized by five components: atherogenic dyslipidemia (elevated triglyceride, low HDL-C, small LDL particles, and commonly, elevated non-HDL-C), elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state. The presence of the metabolic syndrome essentially doubles the risk for CVD. It can be identified clinically by the presence of three or more of the following: abdominal obesity, elevated triglyceride, reduced HDL-C, and elevated blood pressure and glucose (see Table 10.7

Table 10.7 Diagnostic criteria for metabolic syndrome

Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome)	Categorical cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL cholesterol	<40 mg/dL (0.9 mmol/L) in males <50 mg/dL (1.1 mmol/L) in females or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or On drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

* To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

† In the United States, some adults of non-Asian origin (e.g., White, Black, Hispanic) with a marginally increased waist circumference (e.g. 94–101 cm [37–39 in] in men and 80–87 cm [31–34 in] in women) may have a strong genetic contribution to insulin resistance; they should benefit from changes in life habits, similarly to men with categorical increases in waist circumference. A lower waist circumference cutpoint (e.g. ≥90 cm [35 in] in men and ≥80 cm [31 in] in women) appears to be appropriate for persons of Asian origin.

‡ The most commonly used drugs for elevated TG and reduced HDL-C are fibrates and nicotinic acid. A patient on one of these drugs can be presumed to have high TG and low HDL.

Table 10.8 Unresolved issues in cholesterol management

Topic	Unresolved issue	Consensus views
Lifetime risk management	Should cholesterol lowering with drugs be introduced earlier in life?	Epidemiological and genetic studies indicate that a lifetime of low LDL levels is accompanied by very low rates of CHD. However, the long-term safety and tolerance of cholesterol lowering drugs remains to be documented.
Subclincal atherosclerosis imaging for risk assessment	Should arterial imaging be used to select persons for earlier intervention with cholesterol-lowering drugs?	Subclinical atherosclerosis, whether coronary or carotid, is accompanied by increased risk for CVD. However, evidence that wide-spread, routine imaging would be efficacious in prevention of CVD has not been adequately documented. Nonetheless, imaging is promising for risk assessment for properly selected persons.
Emerging risk factors	What is the role of emerging risk factors in global risk assessment for CVD? Examples include apolipoproteins, inflammatory markers, insulin-resistance markers.	Several emerging risk factors have statistical power to predict CVD events. Whether their predictive power is independent of established factors has been controversial. Nonetheless, because of their predictive power physicians have the option of using emerging risk factors as adjunctive predictors in addition to risk-factor assessment with standard risk factors.
Women: ages 45–74 years	Are women candidates for primary prevention with cholesterol-lowering drugs?	Cholesterol-lowering has proven to be efficacious in secondary prevention in women. Primary prevention trials in women have been too limited to draw evidence-based conclusions. Even so, most authorities recommend drug therapy when global risk is high enough to justify drug therapy in men.
Elderly: men ≥ 65 years; women ≥ 75 years	Are older persons candidates for primary prevention with cholesterol-lowering drugs?	Cholesterol-lowering has been proved to be efficacious in secondary prevention in older persons. Primary prevention trials in the elderly have been too limited to draw evidence-based conclusions. Even so, most authorities recommend drug therapy when global risk is high enough to justify drug therapy in middle-aged persons.
Younger adult: men 20–35 years; women 20–45 years	Are younger adults candidates for primary prevention with cholesterol-lowering drugs?	There are no long-term primary prevention trials that start in your adulthood. There is growing interest in use of drugs for lifetime prevention, but at present, drug generally limited to young adults with more severe dyslipidemias.
Different and ethnic groups	Should cholesterol guidelines be applied equally to all ethnic groups?	Most authorities agree that all ethnic groups should be treated equally in spite of a lack of clinical trials in all such groups.

for updated ATP III cutpoints for these factors) [17]. Treatment of the metabolic syndrome places priority on lifestyle therapy (i.e., weight reduction and increased physical activity). For the individual risk factors, treatment should follow currently established guidelines. Subgroup analysis of several clinical trials demonstrate that patients with the metabolic syndrome respond as well or better with CVD risk reduction to established therapies compared to patients without the syndrome.

Other unresolved issues

Table 10.8 addresses a series of issues that have not been resolved. Clinical practice requires that decisions be made regarding the questions addressed. To date clinical trials are limited in these areas. For this reason, clinical judgment is required for treatment decisions. The table outlines current consensus of the experts, although disagreements among authorities can be found in the literature.

Table 10.9 Management of total CVD risk-LIPIDS: European Cardiovascular Guidelines

High risk conditions: Established CVD; type 2 diabetes; type 1 diabetes with microalbuminuria; markedly raised cholesterol levels

- Dietary and exercise advice together with attention to all risk factors comes first
- Aim to reduce total cholesterol to <4.5 mmol/L (~175 mg/dL) or <4 mmol/L (~155 mg/dL) if feasible, and LDL-cholesterol to <2.5 mmol/L (~100 mg/dL) or <2 mmol/L (~8 mg/dL) if feasible
- This may well require statin treatment in many. Some recommend statin for all CVD and most diabetic patients regardless of baseline levels.

SCORE risk >5%

- Lifestyle advice for 3 months, then reassess SCORE risk and fasting lipids
- If SCORE risk remains ≥5%, treat the patient according to recommendations for High Risk Conditions
- If SCORE risk is <5% and total cholesterol is below 5 mmol/L or LDL-cholesterol is <3 mmol/L, treat the patient as if baseline SCORE risk were <5% (see below)

SCORE risk <5%

- Lifestyle advice to reduce total cholesterol <5 mmol/L (<190 mg/dL) and LDL-cholesterol <3 mmol/L (115 mg/dL). Regular follow-up

HDL cholesterol and triglycerides

- Treatment goals are not defined for HDL cholesterol and triglycerides, but HDL cholesterol <1.0 mmol/L (40 mg/dL) for men and <1.2 mmol/L (45 mg/dL) for women and fasting triglycerides of >1.7 mmol/L (150 mg/dL) are markers for increased cardiovascular risk

European guidelines for lipid management

Recently a Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts) issued European guidelines of cardiovascular disease prevention recommendations for clinical practice [18]. Included in these guidelines were recommendations for lipid management. As can be seen in Table 10.9, these recommendations are similar to those of the United States outlined in this chapter. One significant difference however is in the procedure for risk assessment. Risk assessment is done by the so-called SCORE risk chart. This chart emphasized the multifactorial nature of CVD, and it estimates risk for all CVD and not just CHD. It attempts to provide a common language of risk for clinicians. The details of the SCORE risk chart are beyond the scope of the current chapter but are clearly outlined in the primary document [18].

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: Population-Based Prevention of Obesity, http://circ.ahajournals.org/cgi/content/full/118/4/428.

Hypertension

Clive Rosendorff

Introduction
Benefits of lowering BP
BP control rates
Blood pressure measurement in the clinic or the office
Patient evaluation
Laboratory tests and other diagnostic procedures
Treatment
Lifestyle modifications
Pharmacologic treatment
Uncomplicated hypertension
Special considerations
CAD and stable angina
Unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI)
Heart failure
Diabetes
Treatment
Chronic kidney disease (CKD)
Definition of CKD
Hypertension as a risk factor for CKD progression
Hypertension as a consequence of CKD
Lifestyle modifications
Pharmacologic therapy
Endocrine disease and pregnancy
African-Americans
Future directions
Acknowledgements

Introduction

This chapter on hypertension is a summary of, and contains verbatim extracts from, the following guideline statements: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure – JNC 7 (2003) [1,2]; Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Part 1: Blood Pressure Measurement in Humans, a Statement from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research (2005) [3]; Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease; a Scientific Statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention (2007) [4]; Dietary Approaches to Prevent and Treat Hypertension. A Scientific Statement from the American Heart Association (2006) [5]; the American Diabetes Association Guidelines for the Treatment of Hypertension in Adults with Diabetes (2003) [6]; the K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004) [7]; and the Consensus Statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks on the Management of Hypertension in African Americans (2003) [8]. Comparisons will also be made with the guidelines developed in 2007 by the European Society of Hypertension and the European Society of Cardiology [9]. The recommendations for the pharmacologic management of hypertension described in this chapter do not include comprehensive information about antihypertensive drugs; clinicians are strongly advised to read the FDA-approved labeling of each drug before prescribing. In particular each drug has a list of specific contraindications which should be carefully reviewed.

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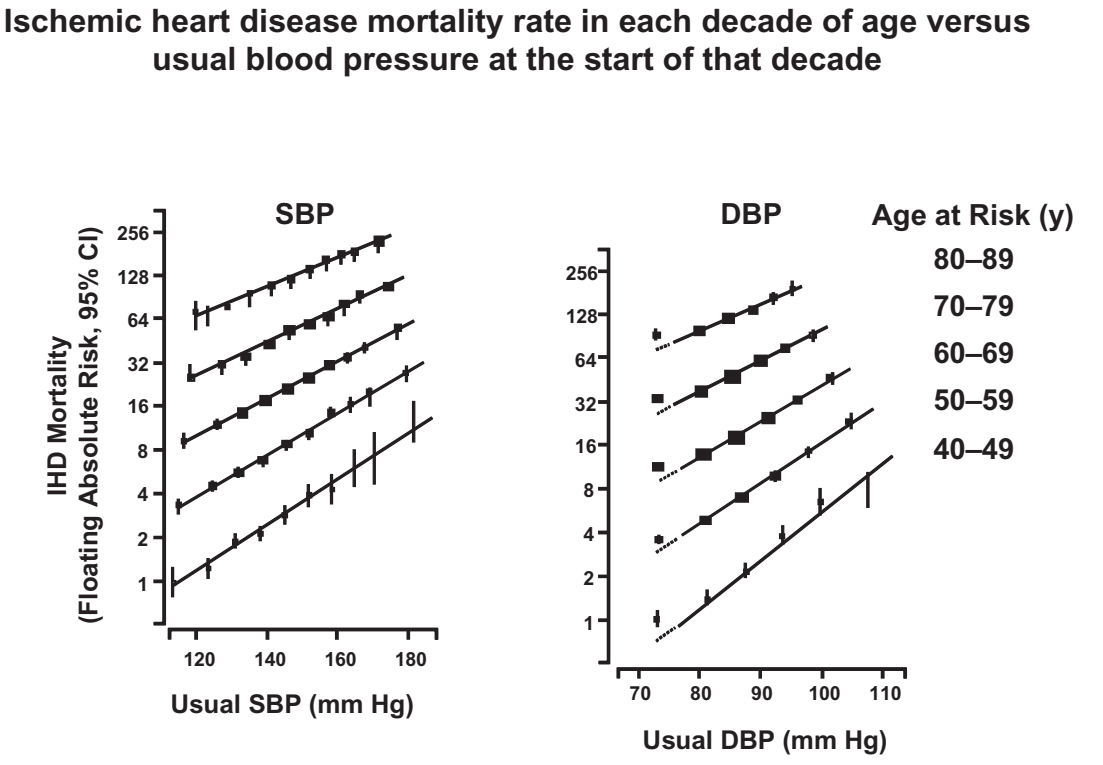
In 2003 the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure – JNC 7 [1,2] was published. The following contains extracts from that report and a summary of some of the major recommendations. Note that these recommendations are 5 years old, and there have been many advances in hypertension research and treatment that warrants an update.

Hypertension, as defined by JNC 7 [1,2] as a systolic blood pressure (SBP) ≥140 mm Hg, or a diastolic blood pressure (DBP) ≥90 mm Hg, and/or current use of antihypertensive medication, affects more than 65 million adult individuals in the United States [10], nearly one-third of the adult population, and approximately 1 billion individuals worldwide. Another one-quarter of US adults have "prehypertension," a SBP of 120–139 mm Hg or DBP of 80 to 89 mm Hg, that is a level above normal but below the hypertensive range. As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented.

The relationship between BP and risk of cardiovascular disease (CVD) events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction, heart failure (HF), stroke, and kidney disease. Data from observational studies involving more than 1 million individuals [11] show a progressive and log-linear relationship between BP and death from ischemic heart disease or stroke, and this relationship is robust from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic and upward, and in all age groups from 40 to 89 years old. For every 20 mm Hg systolic or 10 mm Hg dia-



IHD = ischemic heart disease; CI = confidence interval.

Fig. 11.1 Ischemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade. Reprinted with permission from Lewington *et al*. Lancet. 2002;360:1903–1913.

stolic increase in BP, there is a doubling of mortality from both ischemic heart disease and stroke (Figs 11.1 and 11.2). In addition, longitudinal data obtained from the Framingham Heart Study [12] have indicated that BP values in the 130 to 139/85 to 89 mm Hg range previously considered to be normal but now within the "pre-hypertension" category, are associated with a more than 2-fold increase in relative risk from cardiovascular disease (CVD) compared with those with BP levels below 120/80 mm Hg (Fig. 11.3).

BP changes with increasing age. The rise in SBP continues throughout life, in contrast to DBP, which rises until approximately 50 years old, tends to level off over the next decade, and may remain the same or fall later in life [13] (Fig. 11.4). Diastolic hypertension predominates before 50 years of age, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above the age of 50 years, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important [14].

Table 11.1 is the JNC 7 classification of BP for adults aged 18 years or older. JNC 7 suggests that all people with hypertension (Stages 1 and 2) be treated. At present the treatment goal for BP in individuals with hypertension and no other compelling conditions is <140/90 mm Hg, but is <130/80 mm Hg for patients with diabetes, kidney disease, coronary artery disease, and those with a Framingham 10-year risk score of ≥10%. The goal for individuals with uncomplicated pre-hypertension (120–139/80–89 mm Hg) with no compelling indications for pharmacologic therapy is to lower BP to normal with lifestyle changes and prevent the progressive rise in BP using the recommended lifestyle modifications.

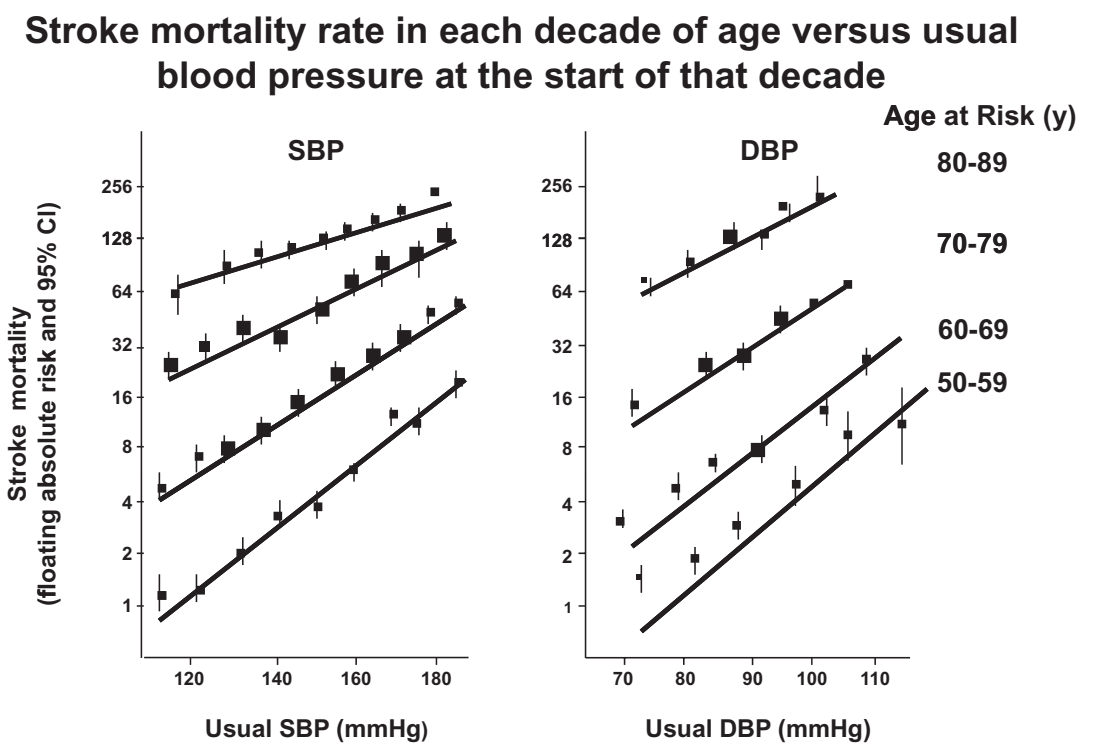
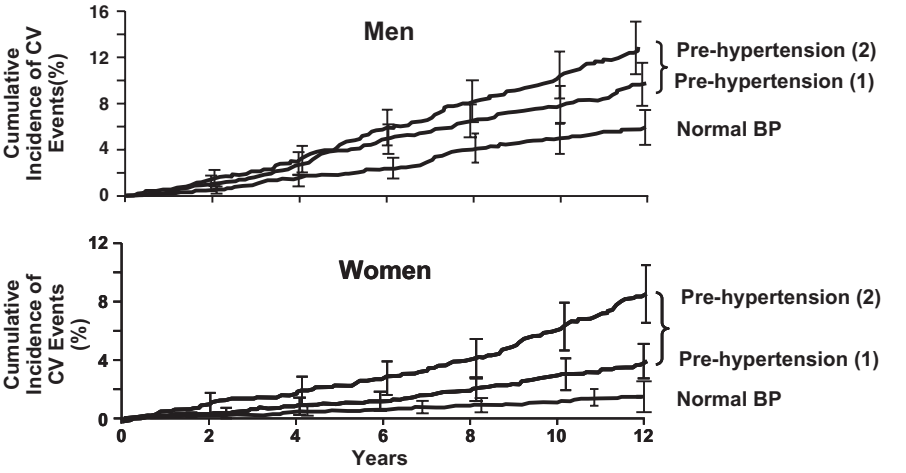


Fig. 11.2 Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade. Reprinted with permission from Lewington *et al*. Lancet. 2002;360:1903–1913.

Impact of Pre-Hypertension on CV Risk



Pre-hypertension (2): 130–139 / 85–89 mm Hg.
Pre-hypertension (1). : 120-129 / 80-84 mm Hg.
Normal BP: <120 / <80 mm Hg.

Fig. 11.3 Impact of blood pressure, not in the hypertensive range, on the risk of cardiovascular disease. Cumulative incidence of cardiovascular events in the Framingham Study in individuals with BP not in the hypertension range. In the figure "Normal BP" is a BP of <120/80 mm Hg (corresponding to "Optimal BP" in the original), "Pre-hypertension 1" is a BP of 120–129/80–84 mm Hg (corresponding to "Low Normal BP"in the original) and "Pre-hypertension 2" is a BP of 130–139/85–89 mm Hg (corresponding to "High Normal BP" in the original). Reproduced, with permission, from Vasan *et al.* N Engl J Med. 2001;345:1291–1297.

Changes of BP with Age.

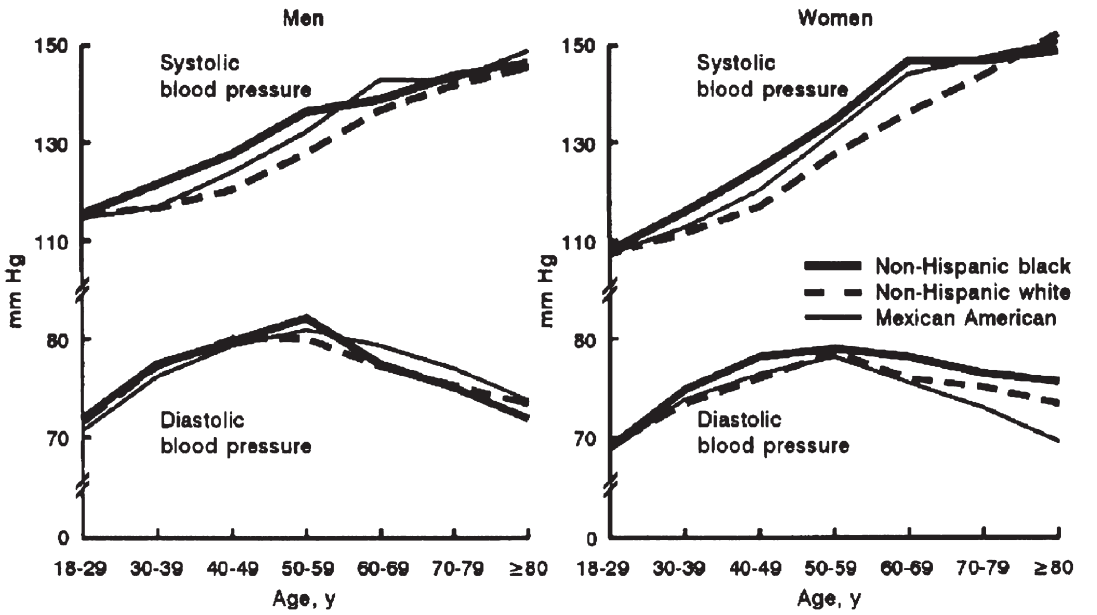


Fig. 11.4 Changes in systolic and diastolic blood pressure with age. SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the US population. Data from NHANES III, 1988 to 1991. Reprinted with permission from Burt, *et al.* Hypertension 1995;23:305–313.

Benefits of lowering BP

In clinical trials, antihypertensive therapy has been associated with 35% to 40% mean reductions in stroke incidence; 20% to 25% in myocardial infarction; and more than 50% in heart failure [15]. It is estimated that in patients with stage 1 hypertension (SBP, 140–159 mm Hg and/or DBP, 90–99 mm Hg) and additional cardiovascular risk factors, achieving a sustained 12 mm Hg decrease in SBP for 10 years will prevent one death for every 11 patients treated. In the presence of cardiovascular disease or target-organ damage, only nine patients would require this BP reduction to prevent a death [16]. However, we do not yet have any outcome studies of treatment of "pre-hypertension" in individuals with blood pressures in the range of 120–139/80–89 mm Hg, although we do know from the Trial of Preventing Hypertension (TROPHY) study [17], that treatment of "pre-hypertension" lowers the likelihood of developing true hypertension, even up to a year after the cessation of treatment.

Table 11.1 Classification of blood pressure for adults

BP classification	Systolic BP	Diastolic BP
Normal	<120	*and* <80
Prehypertension	120–139	*or* 80–89
Stage 1 hypertension	140–159	*or* 90–99
Stage 2 hypertension	≥160	*or* ≥100

Modified, with permission, from Chobanian, *et al.* (2003) [1].

BP control rates

Hypertension is the most common primary diagnosis in the United States. The overall prevalence in 2003–4 was 29.6%. Only two-thirds (66.5%) of those with hypertension were aware that they had it, and of these only about half (53.7%) were being treated at all. Of those on treatment 63.9% were at goal, with a BP ≤140/90 mm Hg [10] (Table 11.2). Simple arithmetic tells us that only about 20% of individuals with hypertension are adequately treated to goal BP. If we were to factor in the even lower BP goals for individuals with diabetes, chronic kidney disease, coronary artery disease and high-risk for cardiovascular disease, the picture is even more dismal. These current control rates are far below the Healthy People 2010 goal of 50%. Recent clinical trials have demonstrated that effective BP control can be achieved in most patients with hypertension, but the majority will require two or more antihypertensive drugs [18].

Blood pressure measurement in the clinic or the office

In 2005 the AHA published "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Part 1: Blood Pressure Measurement in Humans, a Statement from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research" [3]. The following are extracts from that report.

Table 11.2 Awareness, treatment and control among individuals with hypertension in the US population – NHANES 1999–2004

	Prevalence (%)	Awareness (%)	Treatment (%)	Control (treated) (%)
1999–2000	28.6	63.0	47.3	51.3
2001–2002	27.9	62.5	50.1	63.9
2003–2004	29.6	66.5	53.7	63.9

NHANES: National Health and Nutrition Examination Survey.

Date are age adjusted. Hypertension was defined as average BP of 2:140/90 mm Hg or if the individual was taking prescribed antihypertensive medication. "Awareness" refers to those individuals identified as hypertensive and who were aware of the diagnosis, "Treatment" is the percentage of those who were aware that they were hypertensive and who were on antihypertensive medication, and "Control" indicates the percentage of those treated whose BP was <140/90 mm Hg. Adapted, with permission, from Ong, *et al.* (2004) [10].

BP should be measured by an appropriately trained health care provider with a properly calibrated and validated BP instrument, usually either a mercury or aneroid sphygmomanometer. Patients should be seated comfortably and quietly for at least 5 minutes in a chair. The "ideal" sphygmomanometer cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1) [19]. A cuff that is too small for the arm size will overestimate the true BP.

The cuff should be inflated above the systolic BP, and then should be deflated at 2 to 3 mm/s. The first and last audible sounds signal the systolic and diastolic BP. Phase 1 (systolic) and phase 5 (diastolic) Korotkoff sounds are best heard using the bell of the stethoscope over the brachial artery in the antecubital fossa. The BP should be read to the nearest 2 mm Hg, and the tendency to round off the numbers to the nearest 5 or 10 mm Hg ("digit preference") should be resisted. At least two readings should be taken at intervals of at least one minute, and the average of those readings should be recorded as the patient's BP. Sometimes it is useful to measure BP in the standing position, and to compare that with values obtained in the sitting or supine position, especially in the evaluation of dizziness or syncope.

Automated oscillometric BP measuring devices are increasingly being used in office BP measurement, as well as for home and ambulatory monitoring. The potential advantages of automated measurement in the office are the elimination of observer error or digit preference, minimizing the white coat effect, and increasing the number of readings. The main disadvantages are the error inherent in the oscillometric method and the fact that epidemiologic data are mostly based on auscultatory BP measurements.

The standard type of monitor for home use is now an oscillometric device that records pressure from the brachial artery [20]. An up-to-date list of validated monitors is available [21]. Home- or self-monitoring has numerous advantages over ambulatory monitoring, principal among which are that it is relatively cheap and provides a convenient way for monitoring BP over long periods of time. It may also improve therapeutic compliance and BP control. The American Society of Hypertension recommended 135/85 mm Hg as the upper limit of normal for home and ambulatory BP [22].

Devices are now available that have the capacity to store readings in their memory and then transmit them via the telephone to a central server computer, and then to the health care provider. They have the potential to improve patient compliance and hence BP control. Readings taken with a telemonitoring system may correlate more closely than clinic readings with ambulatory BP [23].

Ambulatory blood pressure (ABP) monitoring is a noninvasive, fully automated technique in which BP is recorded over an extended period of time, typically 24 hours. It has been used for many years as a research procedure and has been approved by the Centers for Medicare and Medicaid Services for reimbursement of a single recording in patients with suspected white coat hypertension (WCH), defined as high clinic pressures and normal pressures in other settings, and no evidence of target organ damage. The most common applications are to identify individuals with WCH, or with a BP that is not lower during sleep than awake ("non-dipping pattern"), e.g. in many patients with diabetes, or patients with apparently refractory hypertension but relatively little target organ damage, suspected autonomic neuropathy, and patients in whom there is a large discrepancy between clinic and home measurements of BP. It is also helpful to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, and episodic hypertension. The ABP criteria for the diagnosis of hypertension are a mean BP of more than 135/85 mm Hg while awake and more than 120/75 mm Hg during sleep. In most individuals, BP decreases by 10% to 20% during the night; those in whom such decreases are not present ("non-dippers") are at increased risk for cardiovascular events.

Patient evaluation [1,2]

Evaluation of patients with documented hypertension has three objectives: (1) to reveal identifiable causes of high BP (Table 11.3); (2) to assess the presence or absence of target-organ damage (Table 11.4); and (3) to assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment (Table 11.5). The data needed are acquired through

Table 11.3 Identifiable causes of secondary hypertension

Sleep apnea
Drug-induced or drug-related
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing syndrome
Pheochromocytoma
Coarctation of the aorta
Thyroid or parathyroid disease

Reproduced, with permission, from Chobanian *et al.* (2003) [2].

Table 11.4 Hypertension target-organ damage

Heart
Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

Reproduced, with permission, from Chobanian, *et al.* (2003) [2].

Table 11.5 Major cardiovascular risk factors

Hypertension†
Cigarette smoking
Obesity (BMI ≥30)†
Physical inactivity
Dyslipidemia†
Diabetes mellitus†
Microalbuminuria or estimated GFR <60 mL/min
Age (>55 years for men, >65 years for women)
History of premature cardiovascular disease in first degree relatives (men <55 years or women <65 years)

BMI, Body mass index calculated as weight in kilograms divided by the square of the height in meters.
GFR, Glomerular filtration rate.
† Components of the metabolic syndrome.
Reproduced, with permission, from Chobanian, *et al.* (2003) [2].

the medical history, physical examination, routine laboratory tests, and other diagnostic procedures.

The physical examination should include an appropriate measurement of BP, with verification in the contralateral arm; examination of the optic fundi; body mass index calculated as weight in kilograms divided by the square of height in meters (measurement of waist circumference also may be useful); auscultation for carotid, abdominal, and femoral bruits; palpation of the thyroid gland; thorough examination of the heart and lungs; examination of the abdomen for enlarged kidneys, masses, bruits, and abnormal aortic pulsation; palpation of the lower extremities for edema and pulses; and a neurological assessment.

Laboratory tests and other diagnostic procedures

Routine laboratory tests recommended before initiating therapy include an electrocardiogram; urinalysis; hematocrit; serum potassium, creatinine (or the estimated glomerular filtration rate), and calcium; and blood glucose and a lipid profile (after a 9–12 hour fast) that includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio. More extensive testing for identifiable causes is not indicated generally unless BP control is not achieved.

Treatment

In patients with hypertension with diabetes, chronic kidney disease, coronary artery disease, coronary artery disease equivalents, or a Framingham Risk score of ≥10% in 10 years, the BP goal is ≤130/80 mm Hg [4,6,7]. In hypertensive patients with none of these indications, the goal is <140/90 mm Hg. The European guidelines [9] are essentially in agreement with these recommendations: BP should be lowered to <140/90 mm Hg, but to lower values if tolerated. The European target is also <130/80 mm Hg in diabetics, "or in high or very high-risk patients" such as those with associated conditions (renal disease, stroke, myocardial infarction).

Lifestyle modifications

The reader is referred to the American Heart Association Scientific Statement "Dietary Approaches to Prevent and Treat Hypertension" published in 2006 [5], from which the following recommendations are derived.

A substantial body of evidence strongly supports the concept that many components of the diet can affect BP [5]. Dietary patterns based on the "Dietary Approaches to Stop Hypertension" (DASH) diet [24], which is rich in fruits, vegetables and low-fat dairy foods, with reduced saturated and total fat, together with a reduction in dietary sodium, may help in the management of hypertension. Physical exercise, weight loss in those who are overweight or obese, and moderation of alcohol consumption, have also emerged as appropriate strategies to lower BP (Table 11.6).

African-Americans are especially sensitive to the BP lowering effects of a reduced salt intake, increased potassium intake, and the DASH diet. Older individuals, a group at high-risk for BP-related cardiovascular or renal diseases, can make and sustain dietary changes. In "pre-hypertensive" individuals, dietary changes can lower BP and prevent hypertension. In hypertensive patients dietary changes are an important adjunct to drug therapy.

Pharmacologic treatment

In 2007 the American Heart Association published a Scientific Statement "Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease; a Scientific Statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention" [4]. The following are the recommendations of that Scientific Statement. The reader is referred to the original publication for the clinical trials data and other evidence that support these recommendations. Table 11.7 is a summary of the recommendations.

Uncomplicated hypertension

For the primary prevention of cardiovascular events, renal failure, and other complications of hypertension, aggressive BP lowering is appropriate, with a

Table 11.6 JNC 7 Lifestyle modifications to prevent and manage hypertension

Modification	Recommendation	Approximate SBP reduction (range)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2).	5–20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.	8–14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter-weight persons.	2–4 mm Hg

DASH indicates Dietary Approaches to Stop Hypertension.

For overall cardiovascular risk reduction, stop smoking.

The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

Reproduced, with permission, from Chobanian *et al.* [1].

Table 11.7 Treatment of hypertension in the prevention and management of coronary artery disease

	General CAD Prevention	High CAD Risk*	Stable Angina	UA/NSTEMI	STEMI	LVD
BP target (mm Hg)	<140/90	<130/80				<120/80
Lifestyle modification†	Yes					
Specific drug indications	Any effective anti-hypertensive drug or combination‡	ACEI or ARB *or* CCB *or* Thiazide diuretic *or* Combination	β-B (if patient is hemodynamically stable) *and* ACEI or ARB§			ACEI or ARB *and* β-B *and* Aldosterone antagonist¶ *and* Thiazide or loop diuretic *and* Hydralazine/Isosorbide dinitrate (African-Americans)
Comments	If SBP ≥160 mm Hg or DBP ≥100 mm Hg, then start with two drugs.		If β-B contraindicated, or if side-effects, can substitute diltiazem or verapamil (but not if bradycardia or LVD). Can add dihydropyridine CCB (not diltiazem or varapamil) to β-B. A thiazide diuretic can be added for BP control.			Contraindicated: Verapamil, diltiazem, clonidine, moxonidine, α-blockers

*Diabetes, chronic kidney disease, known CAD or CAD equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurism), or 10-year Framingham risk score of ≥10% (see Fig. 11.5).

†Weight loss if appropriate, healthy diet (including sodium restriction), exercise, smoking cessation, alcohol moderation (see Table 11.6).

‡Evidence supports ACE inhibitor (or ARB), CCB or thiazide diuretic as first line therapy.

§If anterior MI, if hypertension persists, if LV dysfunction or HF, or if the patient has diabetes.

¶If severe HF (NYHA Class III or IV, or EF <40% and clinical heart failure). See text.

Reprinted, with permission, from Rosendorff *et al.* [4].

target BP of <130/80 mm Hg in individuals with any of the following: diabetes mellitus, chronic renal disease, CAD, CAD risk equivalents (carotid artery disease, peripheral arterial disease, aortic aneurysm), and for high-risk patients, defined as those with a 10-year Framingham CAD risk score of ≤10% (Fig. 11.5), and a target BP of <140/90 mm Hg in individuals with none of the above *(Class IIa; Level of Evidence B)*. It is noteworthy that high risk is common in older men; the Framingham database tells us that the prevalence of a greater than 10% risk for CAD in 10 years is about one third in the age group 50–59 years, about two-thirds in 60–69 year-olds and over 90% in those who are 70–79 years [26] (Fig. 11.6).

In patients with an elevated DBP and CAD with evidence of myocardial ischemia, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg if the patient has diabetes mellitus or is over the age of 60 years. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia. In the very old, those over 80 years of age, antihypertensive

Framingham Heart Study: Calculation of the 10-Year CHD Risk in Men and Women.

Men

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280	11	8	5	3	1

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160	2	3

Point Total	10-Year Risk %
<0	<1
0-4	1
5-6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
17	30

10-Year risk _____%

Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280	13	10	7	4	2

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

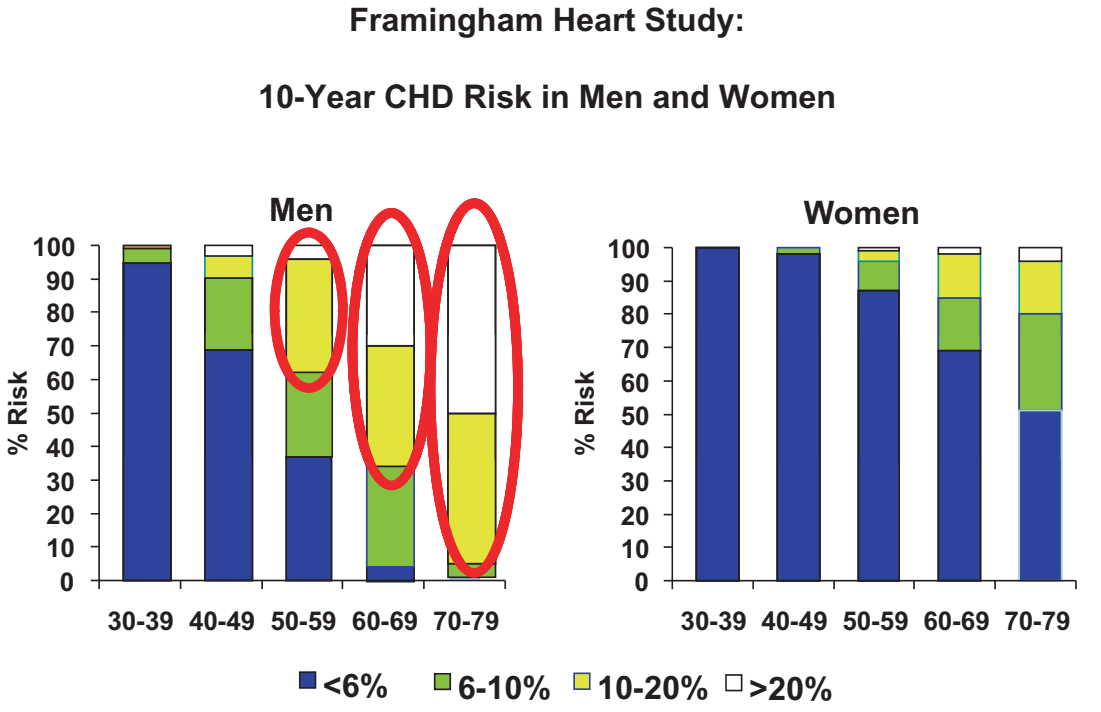
HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160	4	6

Point Total	10-Year Risk %
<9	<1
9-12	1
13-14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
25	30

10-Year risk _____%

Fig. 11.5 Calculating a 10-year risk for coronary heart disease using Framingham point scores. Reprinted from the National Heart, Lung, and Blood Institute as a part of the National Institutes of Health and the US Department of Health and Human Services, NIH Publication No. 01-3305. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm



CHD = coronary heart disease.

Fig. 11.6 Data from the Framingham Heart Study experience. Much of the middle-aged population has a low to intermediate risk for hard CHD events (myocardial infarction or CHD death). Even up to age 80 years, more than three-quarters of women experience a 10-year risk of CHD that falls below 10%. The risks are higher for men, and by age 70 the majority of men are at high risk (>10% per 10 years) for CHD. Nearly all men in the 70–79 year age group are at high risk. Original figure courtesy Peter W. F. Wilson, MD, Framingham Heart Study (unpublished data). Modified, with permission, from Pasternak *et al.* [26].

therapy is effective in reducing stroke risk, but evidence for a reduction in coronary events is less certain *(Class IIa; Level of Evidence C)*.

The choice of drugs remains controversial. There is a general consensus that the amount of BP reduction, rather than the choice of antihypertensive drug, is the major determinant of reduction of cardiovascular risk; however, there is sufficient evidence in the comparative clinical trials to support the use of an ACE inhibitor (or ARB), CCB, or thiazide diuretic as first-line therapy, supplemented by a second drug if BP control is not achieved by monotherapy. Most patients will require two or more drugs to reach goal, and when the BP is >20/10 mm Hg above goal, two drugs should usually be used from the outset either as separate prescriptions or in fixed-dose combinations. β-Blockers should not be used as first-line therapy in uncomplicated hypertension since outcomes are not as good as those with ACE inhibitors, ARBs or CCBs [25]. However, β-blockers are indicated in patients with coronary artery disease for both symptom relief and blood pressure control, and the β-blockers carvedilol, metoprolol and bisoprolol have improved outcomes in patients with heart failure. In the asymptomatic post-MI patient, a β-blocker is a more appropriate choice for secondary prevention for at least 6 months after the infarction and is the drug of first choice if the patient has angina pectoris. (*Class I; Level of Evidence A*). The European guidelines differ [9] from those of the AHA in that β-blockers are included in the list of first-line drugs for any patient except those with metabolic syndrome or at high-risk for incident diabetes. The older JNC 7 guidelines recommend thiazide diuretics as the initial agent for patients who do not have

"compelling indications" for other agents. The JNC 7 recommendations are summarized in Fig. 11.7 and Table 11.8.

Once antihypertensive drug therapy is initiated, most patients should return for follow-up and adjustment of medications at approximately 2–4 weekly intervals until the BP goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. Serum potassium and creatinine should be monitored at least one to two times per year. After BP is at goal and stable, follow-up visits can usually be at 3- to 6-month intervals. Comorbidities, such as HF, associated diseases, such as diabetes, and the need for laboratory tests influence the frequency of visits.

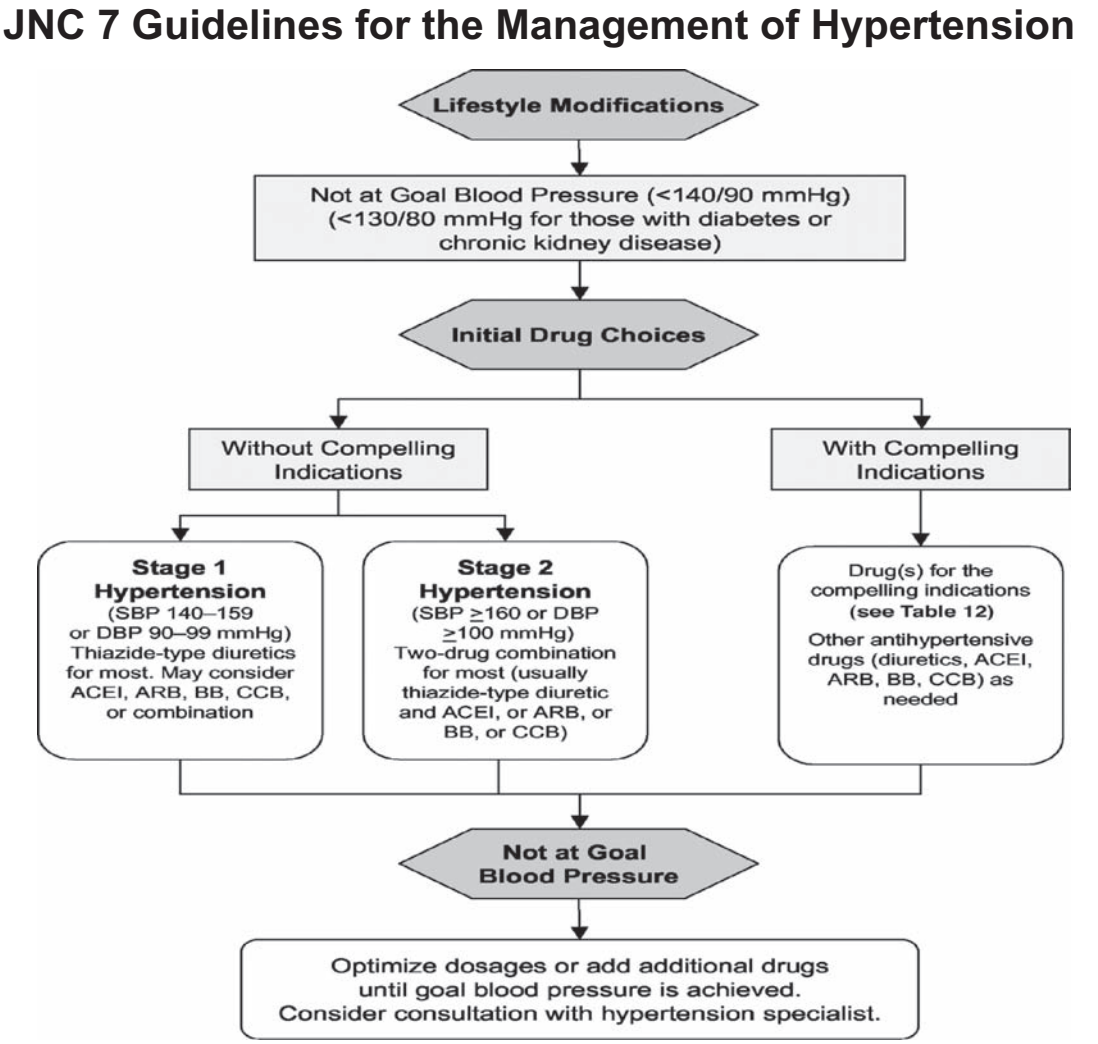


Fig. 11.7 JNC Algorithm for the Management of Hypertension, 2003. "Compelling indications" were shown in Figure 12 of the original JNC 7 report; in this chapter they are shown as Table 11.8. The more recent AHA Scientific Statement on the Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease differs from the JNC 7 guidelines in that recommended first-line therapy for uncomplicated hypertension should be an ACE inhibitor (or ARB), CCB or thiazide diuretic, or a combination of these. β-Blockers are reserved for hypertensive patients with established coronary artery disease. Reprinted, with permission, from Chobanian *et al.* [1].

Table 11.8 JNC 7 Clinical Trial and Guideline basis for compelling indications for individual drug classes

	Recommended drugs						
Compelling Indication*	**Diuretic**	**BB**	**ACEI**	**ARB**	**CCB**	**Aldo Ant**	**Clinical Trial Basis†**
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM
Post-myocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	•	•	•		•		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE, EUROPA, INVEST
Diabetes	•	•	•	•	•		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•			NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	•		•				PROGRESS

BB indicates β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Aldo Ant, aldosterone antagonist.

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes. For references, see Chobanian *et al.* [1]. Reproduced, with permission, from Chabanian *et al.* [1]

Special considerations

CAD and stable angina

Patients with hypertension and chronic stable angina should be treated with a regimen that includes a β-blocker in patients with a history of prior MI, an ACE inhibitor or ARB if there is diabetes mellitus and/or LV systolic dysfunction, and a thiazide diuretic *(Class I; Level of Evidence A)*. The combination of a β-blocker, ACE inhibitor or ARB, and a thiazide diuretic should also be considered in the absence of a prior MI, diabetes mellitus, or LV systolic dysfunction *(Class IIa; Level of Evidence B)*.

If β-blockers are contraindicated or produce intolerable side effects, a non-dihydropyridine CCB (such as diltiazem or verapamil) can be substituted, but not if there is LV dysfunction *(Class IIa; Level of Evidence B)*. If either the angina or the hypertension remains uncontrolled, a long-acting dihydropyridine CCB can be added to the basic regimen of β-blocker, ACE inhibitor, and thiazide diuretic. The combination of a β-blocker and either of the non-dihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic CAD and hypertension because of the increased risk of significant bradyarrhythmias and HF *(Class IIa; Level of Evidence B)*.

The target BP is <130/80 mm Hg. If ventricular dysfunction is present, consideration should be given to lowering the BP even further, to <120/80 mm Hg. In patients with CAD, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia *(Class IIa; Level of Evidence B)*.

There are no special contraindications in hypertensive patients to the use of nitrates, antiplatelet or anticoagulant drugs, or lipid-lowering agents for the management of angina and the prevention of coronary events, except that in uncontrolled severe hypertension in patients who are taking antiplatelet or anticoagulant drugs, BP should be lowered without delay to reduce the risk of hemorrhagic stroke *(Class IIa; Level of Evidence C)*.

Unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI)

In these conditions, the initial therapy of hypertension should include short-acting β1-selective β-blockers without intrinsic sympathomimetic activity, usually intravenously (such as esmolol), in addition to nitrates for symptom control. Oral β-blockers can be substituted at a later stage of the hospital stay *(Class IIa; Level of Evidence B)*. Alternatively, oral β-blockers may be started promptly without prior use of intravenous β-blockers *(Class I; Level of Evidence A)*. If the patient is hemodynamically unstable, the initiation of β-blocker therapy should be delayed until stabilization of HF or shock has been achieved. Diuretics can be added for BP control and for the management of HF *(Class I; Level of Evidence A)*.

If there is a contraindication to the use of a β-blocker, or if the patient develops intolerable side effects of a β-blocker, then a nondihydropyridine CCB, such as verapamil or diltiazem, may be substituted, but not if there is LV dysfunction. If the angina or the hypertension is not controlled with a β-blocker alone, then a longer-acting dihydropyridine CCB may be added. A thiazide diuretic can also be added for BP control *(Class I; Level of Evidence B)*.

If the patient is hemodynamically stable, an ACE inhibitor *(Class I; Level of Evidence A)* or ARB *(Class I; Level of Evidence B)* should be added if the patient has an anterior MI, if hypertension persists, if the patient has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus. ACE inhibitors and ARBs should not be given together because there is an increase in the incidence of adverse events without improving survival.

Aldosterone antagonists may be useful in the management of STEMI with LV dysfunction and HF and may have an additive BP-lowering effect. Serum potassium levels must be monitored. These agents should be avoided in patients with elevated serum creatinine levels (≥2.5 mg/dL in men, ≥2.0 mg/dL in women) or elevated potassium levels (≥5.0 mEq/L) *(Class I; Level of Evidence A)*.

The target BP is <130/80 mm Hg, with the same caveats mentioned above, under "CAD and Stable Angina"*(Class IIa; Level of Evidence B)*.

There are no special contraindications in hypertensive patients to the use of nitrates, anticoagulants, antiplatelet drugs, or lipid-lowering agents for the management of acute coronary syndromes. BP should be lowered without delay in patients with uncontrolled hypertension who are taking antiplatelet or anticoagulant drugs *(Class IIa; Level of Evidence C)*.

Heart failure

The treatment of hypertension in patients with HF should include behavioral modification, such as sodium restriction, and a closely monitored exercise program *(Class I; Level of Evidence C)*. Other nonpharmacological approaches are the same as for patients without HF.

Drugs that have been shown to improve outcomes for patients with HF generally also lower BP. Patients should be treated with diuretics, ACE inhibitors (or ARBs), β-blockers, and aldosterone receptor antagonists *(Class I; Level of Evidence A)*.

Thiazide diuretics should be used for BP control and to reverse volume overload and associated symptoms. In severe HF, or in patients with severe renal impairment, loop diuretics should be used for volume control, but these are less effective than thiazide diuretics in lowering BP. Diuretics should be used together with an ACE inhibitor or ARB and a β-blocker *(Class I; Level of Evidence C)*.

Studies have shown equivalence of benefit of ACE inhibitors and the ARBs candesartan or valsartan in HF. Either class of agents is effective in lowering BP. Drugs from each class can be used together, provided that the patient is hemodynamically stable and not in the immediate post-MI period *(Class I; Level of Evidence A)*.

Among the β-blockers, carvedilol, metoprolol succinate, and bisoprolol have been shown to improve outcomes in HF and are effective in lowering BP *(Class I; Level of Evidence A)*.

The aldosterone receptor antagonists spironolactone and eplerenone have been shown to be beneficial in HF and should be included in the regimen if there is severe HF (New York Heart Association class III or IV, or LVEF <40% and clinical HF). One or the other may be substituted for a thiazide diuretic in patients requiring a potassium-sparing agent. If an aldosterone receptor antagonist is administered with an ACE inhibitor or an ARB or in the presence of renal insufficiency, the serum potassium should be monitored frequently. These drugs should not be

used, however, if the serum creatinine level is ≥2.5 mg/dL in men or ≥2.0 mg/dL in women, or if the serum potassium level is ≥5.0 mEq/L. Spironolactone or eplerenone may be used together with a thiazide diuretic, particularly in patients with refractory hypertension *(Class I; Level of Evidence A)*.

Consider the addition of hydralazine/isosorbide dinitrate to the regimen of diuretic, ACE inhibitor or ARB, and β-blocker in black patients with NYHA class III or IV heart failure *(Class I; Level of Evidence B)*. Others may benefit similarly, but this has not yet been tested.

Drugs to avoid in patients with HF and hypertension are nondihydropyridine CCBs (such as verapamil and diltiazem), clonidine, and moxonidine *(Class III; Level of Evidence B)*. α-Adrenergic blockers, such as doxazosin, should be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses *(Class IIa; Level of Evidence B)*.

The target BP is <130/80 mm Hg, but consideration should be given to lowering the BP even further, to <120/80 mm Hg. The same caveats apply as in "CAD and stable angina" above. *(Class IIa; Level of Evidence B)*.

Diabetes

American Diabetes Association published "Guidelines for the Treatment of Hypertension in Adults with Diabetes" in 2003 [6]. These are the main recommendations:

Blood pressure should be measured at every routine diabetes visit. Patients found to have a BP of ≥130 mm Hg (systolic) or ≥80 mm Hg (diastolic) should have blood pressure confirmed on a separate day. Orthostatic measurement of blood pressure should be performed to assess for the presence of autonomic neuropathy.

Treatment

Patients with diabetes should be treated to a blood pressure <130/80 mm Hg. Patients with a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg should be given lifestyle/behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, should also be treated pharmacologically. Patients with hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) should receive drug therapy in addition to lifestyle/behavioral therapy.

The 2003 American Diabetes Association guidelines suggest that initial drug therapy may be with any drug class currently indicated for the treatment of hypertension, and state, further, that some drug classes (ACE inhibitors, β-blockers, and diuretics) have been repeatedly shown to be particularly beneficial in reducing CVD events during the treatment of uncomplicated hypertension and are therefore preferred agents for initial therapy. However more recent meta-analyses have shown poorer outcomes with β-blockers as initial therapy for patients without coronary artery disease [25]. If ACE inhibitors are not tolerated, ARBs may be used. Additional drugs may be chosen from these classes or another drug class. If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels.

In patients with type 1 diabetes, with or without hypertension, with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with overt diabetic nephropathy, ARB slow the decline in GFR and delay the development of end-stage renal disease. In those with type 2 diabetes, hypertension, macroalbuminuria (>300 mg/day), nephropathy, or renal insufficiency, an ARB should be strongly considered. If one class is not tolerated, the other should be substituted.

In patients over age 55 years, with hypertension or without hypertension but with another cardiovascular risk factor (history of cardiovascular disease, dyslipidemia, microalbuminuria, smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events. In patients with a recent myocardial infarction, β-blockers, in addition, should be considered to reduce mortality.

Chronic kidney disease (CKD)

The National Kidney Foundation developed comprehensive guidelines "Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease" in 2004 [7]. The following are extracts.

Definition of CKD

CKD is defined as kidney damage, as confirmed by kidney biopsy or markers of damage, or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months. Using this definition the Third National Health and Nutrition Examination Survey (NHANES III) database and the US Renal Data System (USRDS) estimates that approximately 11% of adults in the United States have CKD.

Hypertension as a risk factor for CKD progression

There is a strong, consistent relationship of higher levels of blood pressure to faster kidney disease progression. In part, this may be due to deleterious effects of higher intra-glomerular pressure (P_{GC}) which results in an elevated single nephron GFR, which in the short term may lead to stabilization or even increased GFR, but in the long term is followed by proteinuria, glomerular sclerosis, and kidney failure.

Hypertension as a consequence of CKD

Hypertension is a common complication of CKD, which increases the risk for the two main outcomes of CKD: loss of kidney function sometimes leading to kidney failure, and cardiovascular disease (CVD), both associated with increased mortality. Appropriate evaluation and management of hypertension and use of antihypertensive agents in CKD offers the opportunity to slow the progression of kidney disease and reduce the risk of CV. A GFR of <60 mL/min/1.73 m^2 or microalbuminuria (both criteria for the definition of CKD) are independent risk factors for CVD, and the designation of CKD as a "compelling indication" for antihypertensive therapy at a lower BP threshold with a lower BP target (<130/80 mm Hg).

Lifestyle modifications

Dietary and other therapeutic lifestyle modifications are recommended as part of a comprehensive strategy to lower blood pressure and reduce CVD risk in CKD. Dietary sodium intake of less than 2.4 g/d (less than 100 mmol/d) should be recommended in most adults with CKD and hypertension. Other dietary recommendations for adults should be modified according to the stage of CKD, with the DASH diet modified with protein intake 0.6 to 08 g/kg/d, phosphorus 0.8–1.0 g/d and potassium 2–4 g/d for for Stage 3–4 CKD. Other lifestyle modifications include weight maintenance if BMI <25 kg/m^2, weight loss if overweight or obese, moderation of alcohol intake and smoking cessation *(Level of Evidence A)*.

Pharmacologic therapy

All antihypertensive agents can be used to lower blood pressure in CKD. Multi-drug regimens will be necessary in most patients with CKD to achieve therapeutic goals. Patients with specific causes of kidney disease and CVD will benefit from specific classes of agents. Target BP for CVD risk reduction in CKD should be <130/80 mm Hg.

ACE inhibitors and ARBs are the "preferred agents for diabetic kidney disease and nondiabetic kidney disease with spot urine total protein to creatinine ratio of ≥200 mg/g *(Level of Evidence A)*. They should be used at moderate to high doses, as used in clinical trials. Patients treated with ACE inhibitors or ARBs should be monitored for hypotension, decreased GFR and hyperkalemia. The first agent to be added thereafter should be a diuretic. Patients treated with ACE inhibitors or ARBs should be monitored for hypotension, decreased GFR, and hyperkalemia. In most patients the ACE inhibitor or ARB can be continued if (a) the GFR decline over four months is <30% from the baseline value; (b) serum potassium is <5.5 mEq/L *(Level of Evidence B)*. Other drugs which may be used are CCBs or β-blockers.

Thiazide diuretics given once a day are recommended in patients with a GFR ≥30 mL/min/1.73 m^2 and loop diuretics in patients with a GFR <30 mL/min/1.73^2. Loop diuretics may be given in combination with thiazide diuretics for patients with ECF volume expansion and edema. Potassium-sparing diuretics should be used with caution in patients with a GFR <30 mL/min/1.73 m^2, in patients receiving concomitant therapy with ACE inhibitors or ARBs and in patients with additional risk factors for hyperkalemia. Patients treated with diuretics should be monitored for volume depletion, manifested by hypotension or decreased GFR, hypokalemia or other electrolyte abnormalities *(Level of Evidence A)*.

Endocrine disease and pregnancy

The National Kidncy Foundation guidelines also include recommendations for the management of hypertension in patients with endocrine disease and pregnancy. These are summarized in Box 11.1.

Box 11.1 Summary of evidence-based recommendations for management of hypertension in patients with endocrine disease and pregnancy

Indication	Recommendation
Lifestyle modification	Weight loss (in overweight patients)
	Sodium restriction (2.3–3 g/day)
	Potassium intake ≥3.5 g/day
	Alcohol restriction 1 oz/day
	Exercise ≥30 min/day
Type 2 diabetes	Goal BP ≤130/80 mm Hg
	Goal BP ≤120/75 mm Hg when severe proteinuria exists
	ACEI or ARB as first- or second-line agent
	Thiazide diuretic as first- or second-line agent (in low dosage with adequate potassium replacement or sparing)
	β-B (preferably drugs that block both α and β receptors) as second- or third-line agent
	CCB (preferably nondihydropyridine) as second-, third-, or fourth-line agent
Pheochromocytoma	α-Adrenergic blocker as first-line agent, in conjunction with β-B or CCB (or both) as needed
Hyperaldosteronism	Surgical resection for unilateral adenoma
	Aldosterone antagonists, ACEI, or ARB for hyperplasia
	Low-dose glucocorticoid for GRA
Cushing's syndrome	Surgical or ablative therapy for adenoma
	Medical inhibition of steroid synthesis (especially ketoconazole) in intractable cases
Pregnancy	All major antihypertensive agents except ACEI/ARB (preferably methyldopa or nifedipine)
	Magnesium for preeclampsia at high risk for seizures 1–2 A

Reproduced, with permission, from Reference [7]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-adrenergic blocker; BP, blood pressure; CCB, calcium channel blocker; GRA, glucocorticoid-remediable aldosteronism

Box 11.2 Treatment pearls: Management of high blood pressure in African-Americans

- Compared with white Americans, African-Americans are at greater risk for the development of high BP, type 2 diabetes mellitus, coronary heart disease (CHD), heart failure, left ventricular hypertrophy, stroke, and end-stage renal disease.
- These facts suggest the need to obtain BP measurements and assess risk for cardiovascular disease in African-Americans at regular intervals across the lifespan in all primary care settings.
- Clinicians should make concerted efforts to increase awareness among African-Americans of the links between lifestyle choices and cardiovascular and renal outcomes.
- Both high dietary sodium and low dietary potassium intake may contribute to excess high BP in African-Americans. Clinicians should recommend increasing dietary potassium while moderating sodium intake to the recommended <2.4 g/d.
- Obesity and inactivity are particularly prevalent among African-American women and should be viewed as major risk factors in all African-Americans.
- The DASH diet was found to be particularly beneficial in lowering BP in African-Americans. Information about this diet is readily available and should be provided to patients.

- African-Americans have a high prevalence of type 2 diabetes mellitus. Based on current National Cholesterol Education Program guidelines, patients with type 2 diabetes have a CHD risk that is equivalent to patients with CHD and require intensive interventions to lower LDL cholesterol levels to <100 mg/dL (<2.59 mmol/L)
- The perception that it is more medically difficult to lower BP in African-Americans than in other patients is unjustified.
- All antihypertensive drug classes are associated with BP-lowering efficacy in African-Americans, although combination therapy may frequently be required to achieve and maintain target BP.
- As monotherapy, β-blockers and angiotensin-converting enzyme inhibitors may produce less BP-lowering effects in African-Americans.
- Thiazide diuretics and calcium channel blockers may have greater BP-lowering efficacy than do other classes in African-Americans.
- Where compelling indications have been identified for prescribing specific classes of agents, such as β-blockers or renin–angiotensin system blocking agents (ACE inhibitors or angiotensin II receptor blockers), these compelling indications should be applied equally to African-American patients.
- When prescribing ACE inhibitors, it is important to note that compared with whites, African-Americans appear to be at increased risk for ACE inhibitor-associated angioedema, cough, or both. All patients should be instructed to report any symptoms related to angioedema promptly.

Reproduced, with permission, from Reference [8].

African-Americans [8]

In 2003, the Consensus Statement of the Hypertension in African-Americans Working Group of the International Society of Hypertension in Blacks "Management of High Blood Pressure in African-Americans" was published [8]. Box 11.2 is a distillation of the main clinical points.

Future directions

The next important advance will be the generation of the NHLBI-sponsored JNC 8, the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which is still in the earliest stage of its gestation. It is clear that there is a good, evidence-based, trend toward more aggressive treatment of BP to lower goals than ever before, and this will doubtless be incorporated into the JNC 8 recommendations. Another area that is rapidly evolving is the pharmacotherapy of hypertension, with the recent development of new drugs, such as renin inhibitors and vasodilating β-blockers, all of which will need outcomes studies to underpin their utility in the treatment of hypertension. It is highly likely, also, that the new science of pharmacogenomics will aid us in tailoring appropriate therapy to each patient. However, the greatest benefit to the greatest number of people will be achieved by low-technology strategies to ensure that existing treatments are applied to the 80% or so of our population who are hypertensive and are inadequately treated or not treated at all.

Acknowledgements

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References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book these relevant AHA statements and guidelines were published: Ambulatory Blood Pressure Monitoring in Children and Adolescents, http://hyper.ahajournals.org/cgi/reprint/HYPERTENSIONAHA.108.190329; Call to Action on Use and Reimbursement for Home Blood Pressure Monitoring, http://hyper.ahajournals.org/cgi/content/full/52/1/10; Resistant Hypertension: Diagnosis, Evaluation, and Treatment, http://hyper.ahajournals.org/cgi/content/full/51/6/1403; Population-Based Prevention of Obesity, http://circ.ahajournals.org/cgi/content/full/118/4/428.

12 Cardiovascular Disease Prevention in Women

Kathy Berra and Nanette Kass Wenger

Introduction
Summary of key changes
European Guidelines for Cardiovascular Disease Prevention in Clinical Practice
Future directions

Introduction

The American Heart Association (AHA) statistics have, for a number of years, highlighted cardiovascular disease (CVD) as leading cause of death for American women: Hispanic, Black, Asian/Pacific Islander, American Indian/Alaska native and White women. It is well known that, in the United States, more women than men die annually from heart-related illnesses. Women are at great risk both for death and for disability from heart and other diseases of the vascular system [1]. The economic and social costs of heart disease in women are enormous. In the United States, the estimated cost associated with CVD was $448.5 billion, including healthcare and lost productivity in 2008. It is estimated that preventive efforts worldwide would result in 36 million fewer total lives lost due to CVD [2].

The American Heart Association published 2007 updated guidelines for the prevention of CVD in Women, representing the ongoing accumulation of scientific evidence that supports the importance of preventive efforts to reduce death and disability from CVD in women [3]. These new guidelines provide evidence-based practice recommendations to guide appropriate lifestyle and pharmacological interventions for women at all levels of risk.

The risks for developing heart attack and stroke for both women and men are closely related to well-documented cardiovascular risk factors. These include cigarette smoking, abnormal blood lipid levels, hypertension, diabetes, physical inactivity, obesity, unhealthy diet, and depression [1,3–6]. Certain CVD risk factors appear to impart increased risk for women. For example, women with diabetes develop CVD at an earlier age than non-diabetic women and sustain increased morbidity and mortality compared to diabetic men [7,8].

Although CVD predominately affects women over 60 years of age, the risk for developing CVD should be addressed in women of all ages; CVD remains a significant threat for high-risk younger women. Because of this, the new guidelines address the importance of a woman's "lifetime risk" which is greatly influenced by well known CVD risk factors, ethnic diversity and family history. Age plays a major role in the Framingham short-term (10-year) risk calculation for women, which may underestimate risk and thereby disadvantage younger women and women with multiple elevated CVD risk factors. There also may be overestimation or underestimation of risk in non-white populations and an underestimation of younger women with known sub-clinical disease by the Framingham risk score [3].

The Reynolds Risk Score, an algorithm for the calculation of risk CVD in women, has been developed and compared to the traditional Framingham risk score. The Reynolds Risk Score classified 40–50% of all women into higher or lower risk

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Table 12.1 Risk Classification

Risk Classification	Definition
High-Risk	With CAD, CVD, PAD, AAA, CRD*; Framingham Risk Score >20% or High Risk by population-adapted based global risk tool
At Risk	>1 Major Risk Factor# for CVD; evidence of subclinical disease (eg. coronary calcification); poor exercise capacity or poor HR** recovery after exercise
Optimal Risk	<10% Framingham Risk Score; healthy lifestyle; no risk factors

*CAD, coronary heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; AAA, abdominal aortic aneurysm; CRD, chronic renal disease.

**HR (heart rate).

#Cigarette smoking, poor diet, physical inactivity, obesity (especially central adiposity) family history of premature CVD, hypertension, dyslipidemia [3,10].

categories, based on a panel of both traditional and novel risk factors [9].

Limitations of this new algorithm include a lack of information regarding young women, women at low risk, and non-Caucasian women. Accurately estimating *lifetime* CVD risk for women of all ages and ethnicities will help guide educational programs and medical therapies for those at elevated risk.

Although a recent survey of women's awareness, preventive actions and barriers to cardiovascular health showed a doubling in awareness since 1997 [9], less than 50% of women were aware of healthy levels of risk factors. White women were significantly more aware compared to blacks and Hispanics. Importantly, awareness was associated with increased levels of physical activity and weight loss. The survey also found that aware women were more likely to reduce their personal risk factors and those of their family members. Continuing public education and implementation of evidence-based guidelines for women will be important in reducing both death and disability from CVD in women.

Summary of key changes

As in 2004, the 2007 updated Guidelines highlight that favorable lifestyle changes can both decrease cardiovascular risk factors and prevent cardiovascular and coronary heart disease. They further emphasize that the intensity of the intervention should match the woman's level of risk. This emphasis spurred a new risk classification for women – high risk, at risk, or optimal risk (Table 12.1).

The rationale for this new classification is that prevention is important for all women, given their high lifetime cardiovascular risk. One of two women will develop cardiovascular disease in her lifetime. The updated Guideline is aligned with the evidence base, in that most clinical trials providing the evidence involved either high-risk women (those with known cardiovascular disease), or apparently healthy women. It further reflects increased appreciation of the limitations of the Framingham Risk Score, with its narrow focus on 10-year risk, its lack of inclusion of family history, and an underestimation or overestimation of risk in many non-white populations. Further, subclinical disease has been documented among many women who score "low-risk" on the Framingham Risk Score. Lifestyle interventions are the initial approach recommended for all women including a comprehensive risk reduction program. It also reflects expanded indications for rehabilitation of women with vascular diseases (Table 12.2).

A simple algorithm, based on risk status helps guide clinical decision-making and can be shared with women as a basis for their preventive cardiovascular care (see Table 12.3). The American Heart Association's 2007 Guidelines for Preventing Cardiovascular Disease (CVD) in Women, challenges all health professionals to focus on a woman's lifetime CV risk rather than her short-term risk. This important document compels us to begin prevention early, focus on lifestyle and initiate medical therapies as indicated. Tables 12.4–12.9 summarize the recommendations of the 2007 guidelines.

Table 12.2 Selected Recommendations Based on Risk Status

Population	Recommendation
All women	Lifestyle change including smoking cessation. Heart-healthy eating, regular physical activity, weight management.
Women with CVD or stroke*	Rehabilitation program[#]
All women	Lipids and lipoproteins – LDL-C <100 mg/dl, HDL-C >50 mg/dl, and triglycerides <150 mg/dl. Encouraged through lifestyle approaches.
High-risk women	LDL-C lowering drug therapy should be initiated simultaneously with lifestyle interventions.
Very high-risk women with CHD	LDL-C reduction to <70 mg/dl may be reasonable and may require LDL-lowering drug combination.
High-risk women[¶]	75–325 mg of aspirin daily, unless contraindicated, with clopidogrel substituted if aspirin intolerance is present.
Healthy women	81 mg daily or 100 mg every other day of aspirin in women ≥ age 65 should be considered if the blood pressure is controlled and the benefit for ischemic stroke and myocardial infarction prevention outweighs the risk of gastrointestinal bleeding and hemorrhagic stroke.
Healthy women < 65 years of age	Aspirin should be considered for when the benefit for ischemic stroke prevention outweighs the adverse effect of therapy.
Healthy women < 65 years of age	Routine use of aspirin in is not recommended to prevent myocardial infarction.
Hormone replacement therapy (neither hormone therapy nor selective estrogen receptor modulators) in all postmenopausal women	Not recommended for the prevention of CAD or stroke – identified as not useful/effective; may be harmful.
All adult women**	Antioxidant vitamin supplements (vitamins E, C, and beta carotene) and folic acid (with or without vitamin B6 and B12), are not recommended for the primary and secondary prevention of cardiovascular disease.

*To include recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease, or current or prior symptoms of heart failure and a left ventricular ejection fraction below 40% [3,10–13].

[#] Cardiovascular or stroke rehabilitation or a physician-guided home or community-based exercise training program – to include women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease, or current or prior symptoms of heart failure and a left ventricular ejection fraction below 40% [11–14].

[¶] After percutaneous intervention with stent placement or coronary artery bypass grafting within previous year and in women with noncoronary forms of CVD, use current guidelines for aspirin and clopidogrel. [20]

** Folic acid supplementation should be used in the childbearing years to prevent neural tube defects. [4]

CVD indicates cardiovascular disease; MI, myocardial infarction.

Table 12.3 Algorithm for CVD preventive care in women

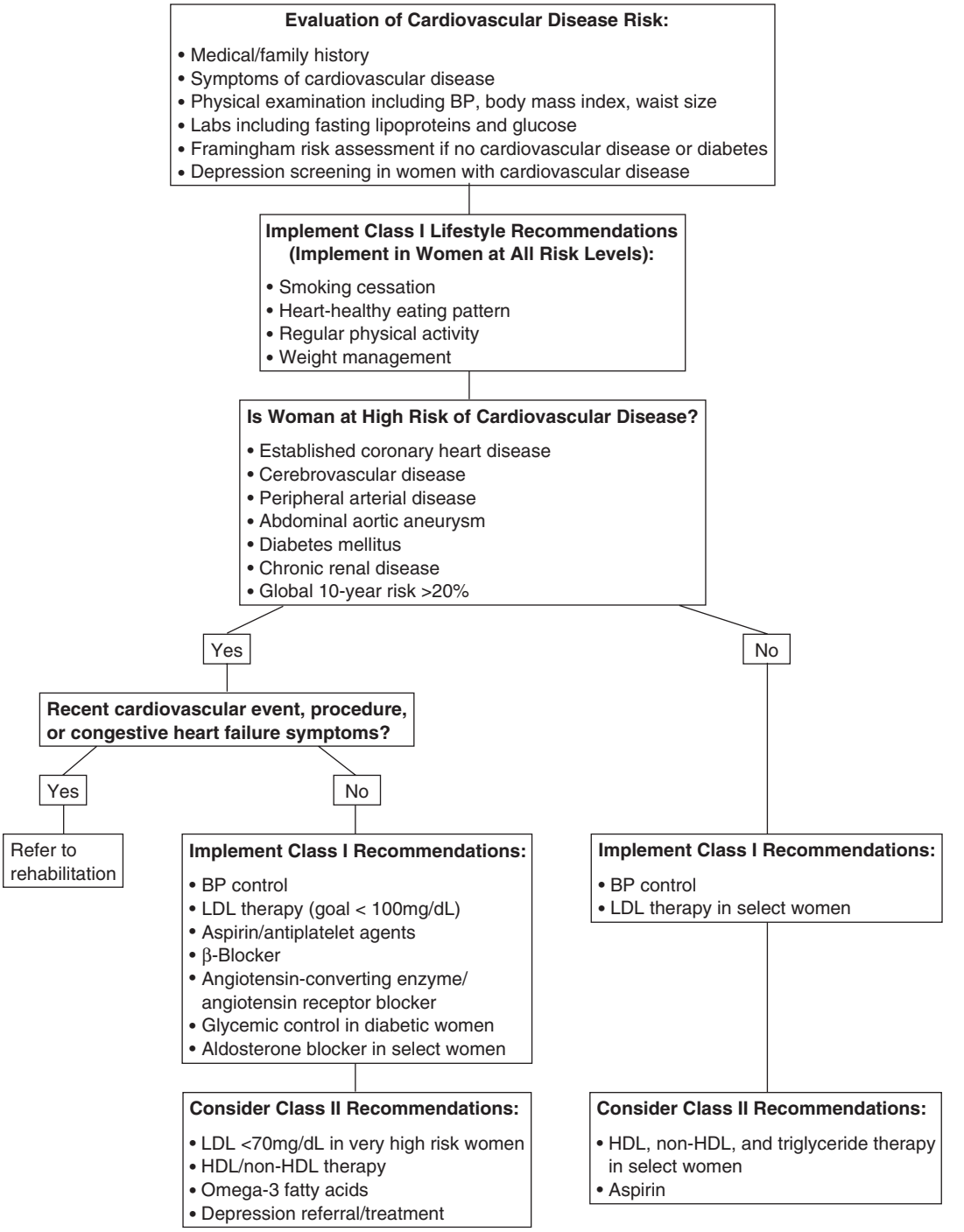

Table 12.4 Guidelines for Prevention of CVD in Women: Clinical Recommendations. Lifestyle interventions – Class I Recommendations

Cigarette smoking

Women should not smoke and should avoid environmental tobacco smoke. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program *(Class I, Level B).*

Physical activity

1 Women should accumulate a minimum of 30 minutes of moderate-intensity physical activity (e.g., brisk walking) on most, and preferably all, days of the week *(Class I, Level B).*

2 Women who need to lose weight or sustain weight loss should accumulate a minimum of 60 to 90 minutes of moderate-intensity physical activity (e.g., brisk walking) on most, and preferably all, days of the week *(Class I, Level C).*

Rehabilitation

A comprehensive risk-reduction regimen, such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program, should be recommended to women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease *(Class I, Level A),* or current/prior symptoms of heart failure and an LVEF <40% *(Class I, Level B).*

Dietary intake

Women should consume a diet rich in fruits and vegetables; choose whole-grain, high-fiber foods; consume fish, especially oily fish,* at least twice a week; limit intake of saturated fat to <10% of energy, and if possible to <7%, cholesterol to <300 mg/d, alcohol intake to no more than 1 drink per day,† and sodium intake to <2.3 g/d (approximately 1 tsp salt). Consumption of trans-fatty acids should be as low as possible (e.g., <1% of energy) *(Class I, Level B).*

Weight maintenance/reduction

Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference <35 in *(Class I, Level B).*

LVEF indicates left ventricular ejection fraction; BMI, body mass index; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CHD, coronary heart disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular disease; and MI, myocardial infarction.

*Pregnant and lactating women should avoid eating fish potentially high in methylmercury (e.g., shark, swordfish, king mackerel, or tile fish) and should eat up to 12 oz/wk of a variety of fish and shellfish low in mercury and check the Environmental Protection Agency and the US Food and Drug Administration's Web sites for updates and local advisories about safety of local catch.

†A drink equivalent is equal to a 12-oz bottle of beer, a 5-oz glass of wine, or a 1.5-oz shot of 80-proof spirits.

Table 12.5 Lifestyle interventions – Class II Recommendations

Omega-3 fatty acids

As an adjunct to diet, omega-3 fatty acids in capsule form (approximately 850 to 1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2 to 4 g) may be used for treatment of women with high triglyceride levels *(Class IIb, Level B).*

Depression

Consider screening women with CHD for depression and refer/treat when indicated *(Class IIa, Level B).*

Table 12.6 Major risk factor interventions – Class I Recommendations

Blood pressure – optimal level and lifestyle

Encourage an optimal blood pressure of <120/80 mm Hg through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products *(Class I, Level B).*

Blood pressure – pharmacotherapy

Pharmacotherapy is indicated when blood pressure is >140/90 mm Hg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes (>130/80 mm Hg). Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases. Initial treatment of high-risk women[‡] should be with β-blockers and/or ACE inhibitors/ARBs, with addition of other drugs such as thiazides as needed to achieve goal blood pressure *(Class I, Level A).*

Lipid and lipoprotein levels – optimal levels and lifestyle

1 The following levels of lipids and lipoproteins in women should be encouraged through lifestyle approaches: LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non–HDL-C (total cholesterol minus HDL cholesterol) <130 mg/dL *(Class I, Level B).*

2 If a woman is at high risk[‡] or has hypercholesterolemia, intake of saturated fat should be <7% and cholesterol intake <200 mg/d) *(Class I, Level B).*

Lipids – pharmacotherapy for LDL lowering, high-risk women

Utilize LDL-C–lowering drug therapy simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C <100 mg/dL *(Class I, Level A)* and similarly in women with other atherosclerotic CVD or diabetes mellitus or 10-year absolute risk → 20% *(Class I, Level B).*

Lipids – pharmacotherapy for LDL lowering, other at-risk women

1 Utilize LDL-C–lowering therapy if LDL-C level is ≥130 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk 10% to 20% *(Class I, Level B).*

2 Utilize LDL-C–lowering therapy if LDL-C level is ≥160 mg/dL with lifestyle therapy and multiple risk factors even if 10-year absolute risk is <10% *(Class I, Level B).*

3 Utilize LDL-C–lowering therapy if LDL ≥190 mg/dL regardless of the presence or absence of other risk factors or CVD on lifestyle therapy *(Class I, Level B).*

Diabetes mellitus

Lifestyle and pharmacotherapy should be used as indicated in women with diabetes *(Class I, Level B)* to achieve an HbA1C less than 7% if this can be accomplished without significant hypoglycemia *(Class I, Level C)*

[‡] Criteria for high risk include established CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic renal disease, diabetes mellitus, and 10-year Framingham risk >20%.

Table 12.7 Major risk factor interventions – Class II

Lipids – pharmacotherapy for LDL lowering – high-risk women

A reduction to <70 mg/dL is reasonable in very-high-risk women[§] with CHD and may require an LDL-lowering drug combination *(Class IIa, Level B).*

Lipids – pharmacotherapy for low HDL or elevated non–HDL, high-risk women

Utilize niacin[‖] or fibrate therapy when HDL-C is low or non–HDL-C is elevated in high-risk women[§] after LDL-C goal is reached *(Class IIa, Level B).*

Lipids – pharmacotherapy for low HDL or elevated non-HDL, other at-risk women

Consider niacin[‖] or fibrate therapy when HDL-C is low or non–HDL-C is elevated after LDL-C goal is reached in women with multiple risk factors and a 10-year absolute risk 10% to 20% *(Class IIb, Level B)*

[§] Criteria for very high risk include established CVD plus any of the following: multiple major risk factors, severe and poorly controlled risk factors, diabetes mellitus.

[‖] Dietary supplement niacin should not be used as a substitute for prescription niacin.

Table 12.8 Preventive drug interventions – Class I and II Recommendations

Class I

Aspirin, high risk

1 Aspirin therapy (75 to 325 mg/d)[¶] should be used in high-risk[‡] women unless contraindicated *(Class I, Level A).*

2 If a high-risk[‡] woman is intolerant of aspirin therapy, clopidogrel should be substituted *(Class I, Level B).*

β-Blockers

β-Blockers should be used indefinitely in all women after MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated *(Class I, Level A).*

ACE inhibitors/ARBs

ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure or an LVEF <40% or with diabetes mellitus *(Class I, Level A).* In women after MI and in those with clinical evidence of heart failure or an LVEF <40% or with diabetes mellitus who are intolerant of ACE inhibitors, ARBs should be used instead *(Class I, Level B).*

Aldosterone blockade

Use aldosterone blockade after MI in women who do not have significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, and have LVEF <40% with symptomatic heart failure *(Class I, Level B).*

Class II

Aspirin – other at-risk or healthy women

In women >65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke *(Class IIa, Level B)* and in women <65 years of age when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy *(Class IIb, Level B).*

[¶] After percutaneous intervention with stent placement or coronary bypass grafting within previous year and in women with noncoronary forms of CVD, use current guidelines for aspirin and clopidogrel.

[‡] Criteria for high risk include established CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic renal disease, diabetes mellitus, and 10-year Framingham risk >20%.

Table 12.9 Class III interventions (not useful/effective and may be harmful) for CVD or MI Prevention in Women

Menopausal therapy

Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD *(Class III, Level A).*

Antioxidant supplements

Antioxidant vitamin supplements (e.g., vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD *(Class III, Level A).*

Folic acid*

Folic acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD *(Class III, Level A).*

Aspirin for MI in women <65 years of age[†]

Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI *(Class III, Level B).*

* Folic acid supplementation should be used in the childbearing years to prevent neural tube defects.

† For recommendation for aspirin to prevent CVD in women ≥65 years of age or stroke in women <65 years of age, see Table 12.8.

European Guidelines for Cardiovascular Disease Prevention in Clinical Practice

The Fourth Joint Task Force of European Society of Cardiology recently published new guidelines for clinicians based on a Systematic Coronary Risk Evaluation (SCORE) system. SCORE estimates 10 year risk of a first *fatal* atherosclerotic event (including heart attack, stroke, aneurysm of the aorta or other) [14]. These new guidelines define gender differences in the public and professional recognition of the size of the problem of CHD in women; in the estimation of total risk in women versus men; and in the need to educate clinicians and the public regarding high absolute risk in a woman's lifetime. Specific issues addressed by the European community include:

- CHD is slightly more common (23% vs. 21%) while stroke is markedly more common (15% vs. 11%) in women compared to men.
- CVD mortality has declined more in men compared to women due in large part to an increase in myocardial infarction in older women.
- Women continue to be underrepresented in clinical trials thus "hampering risk management advice."
- Systolic hypertension is more prevalent in older women, tobacco consumption has fallen more in men compared to women, and smoking associated with use of oral contraceptives increased CHD risk.
- Diabetes confers a considerably greater risk in women compared to men (self-reported diabetes increases the 10-year risk of a fatal heart attack by five times in women compared to three times in men).
- Obesity is more common in middle aged women and the metabolic syndrome is more common in women with CHD compared to men.
- Low absolute risk in younger women may be "falsely reassuring" in light of the relative risk chart.
- Hormone replacement therapy is not advised for preventive purposes.
- Atypical chest pain syndrome in women creates a disadvantage due to lower frequency of diagnostic testing and difficulty in interpretation.
- Women have a higher in-hospital mortality for acute coronary syndrome [14].

Future directions

Women's risk of death and disability from CHD is a worldwide pandemic. Implementation of the new guidelines for preventive CVD care for women will require intense efforts on the part of the government, the public and healthcare professionals.

Research efforts are needed to improve the evaluation, diagnosis and treatment of women with chest pain syndromes**.** Data from the WISE Study indicates that some women with chest pain and without significant epicardial disease by angiography, remain at high risk for a cardiac event. Improving the ability to identify women at risk will require advances in our understanding of gender based pathophysiology of vascular disease. Gender specific evaluation and treatment will follow these discoveries [15]. Along with this must come increased efforts to understand differences in risk and treatment of CVD in older women, in ethnic populations.

Type 2 Diabetes confers significantly worse risk for CVD morbidity and mortality in women compared to men [16,17]. Defining the synergy between elevated blood glucose and other CVD risk factors in women must be a national research priority. This will require increased inclusion of women in all cardiovascular clinical trials to provide a more robust evidence base, with gender-specific reporting of outcomes. Efforts to improve lifestyles and reduce risk factors in women with diabetes and those with risk factors for diabetes also must be intensified. Along with these efforts must come a continuing emphasis on guideline-based intervention and care.

Further research efforts in the evaluation of depression and its relationship to CVD outcomes in women need to be undertaken. The ENRICHD Trail demonstrated that for women and men with heart disease, depression confers additional mortality risk [18].

Ongoing research to develop a CVD algorithm that more accurately predicts lifetime risk for CVD in women is critical in our overall ability to identify women at high lifetime risk and target appropriate treatments. There is convincing evidence that risk factors for CVD are found clustered in families as a result of both lifestyle and genetics. In addition, there is evidence that awareness of this risk by women increases the likelihood that family-based

lifestyle changes to prevent CVD will be implemented.

The past decade has witnessed an enormous increase in public education regarding women's risk for CVD – these efforts are to be commended and intensified. With the combined efforts of ongoing research, development and implementation of evidence-based guidelines, healthcare provider education and a continuing focus on women's heart health by the media, we might turn the tide of the major cause of death and disability on women. Public and professional organizations such as the American Heart Association (Go Red for Women), the National Heart Lung and Blood Institute (the Heart Truth Campaign), the WomenHeart (the leading support organization for women with heart disease), and the Society for Women's Health Research are to be commended and supported in their continuing public education and support for women at risk and for those with heart disease.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: Population-Based Prevention of Obesity, http://circ.ahajournals.org/cgi/content/full/118/4/428.

13

Heart Failure

Sharon A. Hunt and Mariell Jessup

Guidelines for the diagnosis and management of chronic heart failure in the adult
Review
Recommendations for the diagnosis and management of chronic heart failure in the adult
Initial and serial clinical assessment of patients presenting with HF
Recommendations for the initial clinical assessment of patients presenting with HF
Recommendations for serial clinical assessment of patients presenting with HF
Therapy for heart failure
Recommendations for Stage A – patients at high risk for developing HF
Recommendations for Stage B – patients with cardiac structural abnormalities or remodeling who have not developed HF symptoms
Stage C – patients with current or prior symptoms of HF
Recommendations for patients with reduced LVEF
Recommendations for patients with HF and normal LVEF
Recommendations for Stage D – patients with refractory end-stage HF
Treatment of special populations
Recommendations
Patients with HF who have concomitant disorders
Recommendations
End-of-life considerations
Recommendations
Performance measures and standards
A comparison of the ACC/AHA Guidelines with other recommendations
Future directions

The AHA Guidelines and Scientific Statements Handbook
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Guidelines for the diagnosis and management of chronic heart failure in the adult [1]

Review

Heart failure (HF) is a major and growing public health problem in the United States. Approximately 5.3 million patients in this country have HF, and 660,000 patients are diagnosed with HF for the first time each year. The disorder is the primary reason for 3.4 million office visits and 5.5 million hospital days each year. From 1990 to 1999, the annual number of hospitalizations has increased from approximately 720,000 to over 1 million for HF as a primary diagnosis and 4.2 million for HF all-listed diagnosis. In 2004, over 284,000 patients died of HF as total mention mortality. The number of total mention HF deaths in 1994 was as high as it was in 2004.

Heart failure is primarily a condition of the elderly, and thus the widely recognized "aging of the population" also contributes to the increasing incidence of HF. The incidence of HF approaches 10 per 1000 population after age 65, and approximately 80% of patients hospitalized with HF are more than 65 years old. Heart failure is the most common Medicare diagnosis-related group (i.e., hospital discharge diagnosis), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis. It has been estimated that in 2008, the total direct and indirect cost of HF in the US will be equal to $34.8 billion.

Recommendations for the diagnosis and management of chronic heart failure in the adult

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format and shown in Table 13.1. Recommendations are

Table 13.1 ACC/AHA Class of Recommendation and Level of Evidence Table

Estimate of Certainty (Precision) of Treatment Effect	Size of treatment effect			
	Class I	**Class IIa**	**Class IIb**	**Class III**
	Benefit >>> Risk	***Benefit >> Risk***	***Benefit ≥ Risk***	***Risk ≥ Benefit***
		Additional studies with focused objectives needed	***Additional studies with broad objectives needed; Additional registry data would be helpful***	***No additional studies needed***
	Procedure/Treatment SHOULD be performed/administered	**IT IS REASONABLE to perform procedure/administer treatment**	**Procedure/Treatment MAY BE CONSIDERED**	**Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
Level A *Multiple (3–5) population risk strain evaluated** *General consistency of direction and magnitude of effect*	• Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence form multiple randomized trials or meta-analyses
Level B *Limited (2–3) population risk strain evaluated**	• Recommendation that procedure or treatment is useful/effective • Limited evidence from single randomized trial or non-randomized studies	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from single randomized trial or non-randomized studies	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from single randomized trial or non-randomized studies	• Recommendation that procedure or treatment not useful/effective and may be harmful • Limited evidence from single randomized trial or non-randomized studies
Level C *Very Limited (1–2) population risk strain evaluation**	• Recommendation that procedure or treatment is useful/effective • Only expert opinion, case studies, or standard-of-care	• Recommendation in favor of treatment or procedure being useful/effective • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation's usefulness/efficacy less well established • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation that procedure or treatment not useful/effective and may be harmful • Only expert opinion, case studies, or standard-of-care
Suggested phrases for writing recommendations†	shoud is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/ uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

* Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use.
†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full indent of the recommendation. It is hoped that this will increase reader's comprehension of the guidelines and will allow queries at the individual recommendation level.

evidence based and derived primarily from published data. The reader is referred to the full-text guidelines for a complete description of the rationale and evidence supporting these recommendations.

Initial and serial clinical assessment of patients presenting with HF

Recommendations for the initial clinical assessment of patients presenting with HF

Class I

1 A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. *(Level of Evidence: C)*

2 A careful history of current and past use of alcohol, illicit drugs, current or past standard or "alternative therapies," and chemotherapy drugs should be obtained from patients presenting with HF. *(Level of Evidence: C)*

3 In patients presenting with HF, initial assessment should be made of the patient's ability to perform routine and desired activities of daily living. *(Level of Evidence: C)*

4 Initial examination of patients presenting with HF should include assessment of the patient's volume status, orthostatic blood pressure changes, measurement of weight and height, and calculation of body mass index. *(Level of Evidence: C)*

5 Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, fasting blood glucose (glycohemoglobin), lipid profile, liver function tests, and thyroid-stimulating hormone. *(Level of Evidence: C)*

6 Twelve-lead electrocardiogram and chest radiograph (PA and lateral) should be performed initially in all patients presenting with HF. *(Level of Evidence: C)*

7 Two-dimensional echocardiography with Doppler should be performed during initial evaluation of patients presenting with HF to assess LVEF, LV size, wall thickness, and valve function. Radionuclide ventriculography can be performed to assess LVEF and volumes. *(Level of Evidence: C)*

8 Coronary arteriography should be performed in patients presenting with HF who have angina or significant ischemia unless the patient is not eligible for revascularization of any kind. *(Level of Evidence: B)*

Class IIa

1 Coronary arteriography is reasonable for patients presenting with HF who have chest pain that may or may not be of cardiac origin who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization. *(Level of Evidence: C)*

2 Coronary arteriography is reasonable for patients presenting with HF who have known or suspected coronary artery disease but who do not have angina unless the patient is not eligible for revascularization of any kind. *(Level of Evidence: C)*

3 Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with HF who have known coronary artery disease and no angina unless the patient is not eligible for revascularization of any kind. *(Level of Evidence: B)*

4 Maximal exercise testing with or without measurement of respiratory gas exchange and/or blood oxygen saturation is reasonable in patients presenting with HF to help determine whether HF is the cause of exercise limitation when the contribution of HF is uncertain. *(Level of Evidence: C)*

5 Maximal exercise testing with measurement of respiratory gas exchange is reasonable to identify high-risk patients presenting with HF who are candidates for cardiac transplantation or other advanced treatments. *(Level of Evidence: B)*

6 Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. *(Level of Evidence: C)*

7 Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases. *(Level of Evidence: C)*

8 Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy. *(Level of Evidence: C)*

9 Measurement of B-type natriuretic peptide (BNP)* can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. *(Level of Evidence: A)*

Class IIb

1 Noninvasive imaging may be considered to define the likelihood of coronary artery disease in patients with HF and LV dysfunction. *(Level of Evidence: C)*
2 Holter monitoring might be considered in patients presenting with HF who have a history of MI and are being considered for electrophysiologic study to document VT inducibility. *(Level of Evidence: C)*

Class III

1 Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF. *(Level of Evidence: C)*
2 Routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with HF. *(Level of Evidence: C)*
3 Routine measurement of circulating levels of neurohormones (e.g., norepinephrine or endothelin) is not recommended for patients presenting with HF. *(Level of Evidence: C)*

Recommendations for serial clinical assessment of patients presenting with HF

Class I

1 Assessment should be made at each visit of the ability of a patient with HF to perform routine and desired activities of daily living. *(Level of Evidence: C)*
2 Assessment should be made at each visit of the volume status and weight of a patient with HF. *(Level of Evidence: C)*
3 Careful history of current use of alcohol, tobacco, illicit drugs, "alternative therapies," and chemotherapy drugs, as well as diet and sodium intake, should be obtained at each visit of a patient with HF. *(Level of Evidence: C)*

Class IIa

Repeat measurement of EF and the severity of structural remodeling can provide useful information in patients with HF who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. *(Level of Evidence: C)*

Class IIb

The value of serial measurements of BNP* to guide therapy for patients with HF is not well established. *(Level of Evidence: C)*

Therapy for heart failure

Table 13.2 describes cardiovascular medications useful for treatment of various stages of HF.

Recommendations for Stage A – patients at high risk for developing HF

Class I

1 In patients at high risk for developing HF, systolic and diastolic hypertension should be controlled in accordance with contemporary guidelines. *(Level of Evidence: A)*
2 In patients at high risk for developing HF, lipid disorders should be treated in accordance with contemporary guidelines. *(Level of Evidence: A)*
3 For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines. *(Level of Evidence: C)*
4 Patients at high risk for developing HF should be counseled to avoid behaviors that may increase the risk of HF (e.g., smoking, excessive alcohol consumption, and illicit drug use). *(Level of Evidence: C)*
5 Ventricular rate should be controlled or sinus rhythm restored in patients with supraventricular tachyarrhythmias who are at high risk for developing HF. *(Level of Evidence: B)*
6 Thyroid disorders should be treated in accordance with contemporary guidelines in patients at high risk for developing HF. *(Level of Evidence: C)*
7 Healthcare providers should perform periodic evaluation for signs and symptoms of HF in patients at high risk for developing HF. *(Level of Evidence: C)*

*The writing committee intended BNP to indicate B-type natriuretic peptide rather than a specific type of assay. Assessment can be made using assays for BNP or N-terminalproBNP. The two types of assays yield clinically similar information.

Table 13.2 Cardiovascular medications useful for treatment of various stages* of HF

Drug	Stage A	Stage B	Stage C
Ace inhibitors			
Benazepril	H	–	–
Captopril	H, DN	Post MI	HF
Enalapril	H, DN	HF	HF
Fosinopril	H	–	HF
Lisinopril	H, DN	Post MI	HF
Moexipril	H	–	–
Penindopril	H, CV Risk	–	–
Quinapril	H	–	HF
Ramipril	H, CV Risk	Post MI	Post MI
Trandolapril	H	Post MI	Post MI
Angiotensin receptor blockers			
Candesartan	H	–	HF
Eprosartan	H	–	–
Irbesartan	H, DN	–	–
Losartan	H, DN	CV Risk	–
Olmesartan	H	–	–
Telmisartan	H	–	–
Valsartan	H, DN	Post MI	Post MI, HF
Aldosterone blockers			
Eplerenone	H	Post MI	Post MI
Spironolactone	H	–	HF
Beta-blockers			
Acebutolol	H	–	–
Atenolol	H	Post MI	–
Betaxolol	H	–	–
Bisoprolol	H	–	HF
Carteolol	H	–	–
Carvedilol	H	Post MI	HF, Post MI
Labetalol	H	–	–
Metoprolol succinate	H	–	HF
Metoprolol tartrate	H	Post MI	–
Nadolol	H	–	–
Penbutolol	H	–	–
Pindolol	H	–	–
Propranolol	H	Post MI	–
Timolol	H	Post MI	–
Digoxin	–	–	HF

*See Figure 13.1 for explanation of stages of heart failure.

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure and asymptomatic left venricular dysfunction; Post MI, reduction in heart failure-or other cardiac events following myocardial infarction.

8 In patients at high risk for developing HF who have known atherosclerotic vascular disease, healthcare providers should follow current guidelines for secondary prevention. *(Level of Evidence: C)*

9 Healthcare providers should perform a noninvasive evaluation of LV function (i.e., LVEF) in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. *(Level of Evidence: C)*

Class IIa

1 Angiotensin-converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. *(Level of Evidence: A)*

2 Angiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. *(Level of Evidence: C)*

Class III

Routine use of nutritional supplements solely to prevent the development of structural heart disease should not be recommended for patients at high risk for developing HF. *(Level of Evidence: C)*

Recommendations for Stage B – patients with cardiac structural abnormalities or remodeling who have not developed HF symptoms

Class I

1 All Class I recommendations for Stage A should apply to patients with cardiac structural abnormalities who have not developed HF. (*Levels of Evidence: A, B, and C as appropriate)*

2 Beta-blockers and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF (see Table 13.3). *(Level of Evidence: A)*

3 Beta-blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (see Table 13.3 and text). *(Level of Evidence: C)*

4 Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no

Table 13.3 Oral diuretics recommended for use of fluid retention in HF

Drug	Initial daily dose(s)	Maximum total daily dose	Duration of action
Loop diuretics			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
Thiazide diuretics			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
Potassium-sparing diuretics			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg*	2 to 3 hours
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
Sequential nephron blockade			
Metolazone	2.5 to 10 mg once plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic		

mg indicates milligrams; IV, intravenous.

*Higher doses may occasionally be used with close monitoring.

symptoms of HF, even if they have not experienced MI. *(Level of Evidence: A)*

5 An ARB should be administered to post-MI patients without HF who are intolerant of ACEIs and have a low LVEF. *(Level of Evidence: B)*

6 Patients who have not developed HF symptoms should be treated according to contemporary guidelines after an acute MI. *(Level of Evidence: C)*

7 Coronary revascularization should be recommended in appropriate patients without symptoms of HF in accordance with contemporary guidelines (see ACC/AHA Guidelines for the Management of Patients with Chronic Stable Angina). *(Level of Evidence: A)*

8 Valve replacement or repair should be recommended for patients with hemodynamically significant valvular stenosis or regurgitation and no symptoms of HF in accordance with contemporary guidelines. *(Level of Evidence: B)*

Class IIa

1 Angiotensin converting enzyme inhibitors or ARBs can be beneficial in patients with hypertension and LVH and no symptoms of HF. *(Level of Evidence: B)*

2 Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs. *(Level of Evidence: C)*

3 Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIb

Placement of an ICD might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year. *(Level of Evidence: C)*

Class III

1 Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit. *(Level of Evidence: C)*

2 Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of HF is not recommended. *(Level of Evidence: C)*

3 Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (see text in Stage C). *(Level of Evidence: C)*

Stage C – patients with current or prior symptoms of HF

Recommendations for patients with reduced LVEF

Class I

1 Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. *(Levels of Evidence: A, B, and C as appropriate)*

2 Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (see Table 13.4). *(Level of Evidence: C)*

3 Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 13.3 and text). *(Level of Evidence: A)*

4 Beta-blockers (using one of the three proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (see Table 13.3 and text). *(Level of Evidence: A)*

5 Angiotensin II receptor blockers approved for the treatment of HF (see Table 13.3) are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant (see text for information regarding patients with angioedema). *(Level of Evidence: A)*

6 Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text). *(Level of Evidence: B)*

7 Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF. *(Level of Evidence: B)*

Table 13.4 ACC/AHA Heart Failure Performance Measures: inpatient measure descriptions

Performance measure name	Measure description
1. Evaluation of left ventricular systolic (LVS) function	Heart failure patients with documentation in the hospital record that LVS function was assessed before arrival, during hospitalization, or is planned after discharge.
2. ACE inhibitor (ACEI), or angiotensin receptor blocker (ARB) for LVSD	Heart failure patients with LVSD and without both ACEI and ARB contraindications who are prescribed an ACEI or ARB at hospital discharge.
3. Anticoagulant at discharge for HF patients with atrial fibrillation (AF)	Heart failure patients with chronic/recurrent AF and without warfarin contraindications who are prescribed warfarin at discharge.
4. Discharge instructions	Heart failure patients discharged home with written instructions or educational material given to patient or caregiver at discharge or during the hospital stay addressing *all* of the following: activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen.
5. Adult smoking cessation advice/counseling	Heart failure patients with a history of smoking cigarettes, who are given smoking cessation advice or counseling during hospital stay.

8 An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in patients with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. *(Level of Evidence: A)*

9 Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with ischemic heart disease who are at least 40 days post-MI, have an LVEF less than or equal to 30%, with NYHA functional Class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*

10 Implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with nonischemic cardiomyopathy who have an LVEF less than or equal to 30%, with NYHA functional Class II or III symptoms while undergoing chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

11 Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional Class III or ambulatory Class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 0.12 ms, should receive cardiac resynchronization therapy unless contraindicated. *(Level of Evidence: A)*

12 Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. *(Level of Evidence: B)*

Class IIa

1 Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. *(Level of Evidence: A)*

2 Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. *(Level of Evidence: B)*

3 The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. *(Level of Evidence: A)*

4 Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of 30% to 35% of any origin with NYHA functional Class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year. *(Level of Evidence: B)*

Class IIb

1 A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. *(Level of Evidence: C)*

2 The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. *(Level of Evidence: B)*

Class III

1 Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. *(Level of Evidence: C)*

2 Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF. *(Level of Evidence: A)*

3 Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended for patients with current or prior symptoms of HF and reduced LVEF, except as palliation for patients

with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for Stage D). *(Level of Evidence: C)*

4 Use of nutritional supplements as treatment for HF is not indicated in patients with current or prior symptoms of HF and reduced LVEF. *(Level of Evidence: C)*

5 Hormonal therapies other than to replete deficiencies are not recommended and may be harmful to patients with current or prior symptoms of HF and reduced LVEF. *(Level of Evidence: C)*

Recommendations for patients with HF and normal LVEF

Class I

1 Physicians should control systolic and diastolic hypertension in patients with HF and normal LVEF, in accordance with published guidelines. *(Level of Evidence: A)*

2 Physicians should control ventricular rate in patients with HF and normal LVEF and atrial fibrillation. *(Level of Evidence: C)*

3 Physicians should use diuretics to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF. *(Level of Evidence: C)*

Class IIa

Coronary revascularization is reasonable in patients with HF and normal LVEF and coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function. *(Level of Evidence: C)*

Class IIb

1 Restoration and maintenance of sinus rhythm in patients with atrial fibrillation and HF and normal LVEF might be useful to improve symptoms. *(Level of Evidence: C)*

2 The use of beta-adrenergic blocking agents, ACEIs, ARBs, or calcium antagonists in patients with HF and normal LVEF and controlled hypertension might be effective to minimize symptoms of HF. *(Level of Evidence: C)*

3 The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established. *(Level of Evidence: C)*

Recommendations for Stage D – patients with refractory end-stage HF

Class I

1 Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF. *(Level of Evidence: B)*

2 Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF. *(Level of Evidence: B)*

3 Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful. *(Level of Evidence: A)*

4 Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies. *(Level of Evidence: C)*

5 Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate defibrillation. *(Level of Evidence: C)*

Class IIa

Consideration of an LV assist device as permanent or "destination" therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy. *(Level of Evidence: B)*

Class IIb

1 Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms. *(Level of Evidence: C)*

2 The effectiveness of mitral valve repair or replacement is not established for severe secondary mitral regurgitation in refractory end-stage HF. *(Level of Evidence: C)*

3 Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF. *(Level of Evidence: C)*

Class III

1 Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF. *(Level of Evidence: C)*

2 Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF. *(Level of Evidence: B)*

Treatment of special populations

Recommendations

Class I

1 Groups of patients including (a) high-risk ethnic minority groups (e.g., blacks); (b) groups underrepresented in clinical trials; and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population. *(Level of Evidence: B)*

2 It is recommended that evidence-based therapy for HF be used in the elderly patient, with individualized consideration of the elderly patient's altered ability to metabolize or tolerate standard medications. *(Level of Evidence: C)*

Class IIa

The addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested. *(Level of Evidence: A)*

Patients with HF who have concomitant disorders

Recommendations

Class I

1 All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions. *(Level of Evidence: C)*

2 Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines. *(Level of Evidence: C)*

3 Physicians should use nitrates and beta-blockers for the treatment of angina in patients with HF. *(Level of Evidence: B)*

4 Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina. *(Level of Evidence: A)*

5 Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event. *(Level of Evidence: A)*

6 Physicians should control the ventricular response rate in patients with HF and atrial fibrillation with a beta-blocker (or amiodarone, if the beta-blocker is contraindicated or not tolerated). *(Level of Evidence: A)*

7 Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina. *(Level of Evidence: C)*

8 Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to prescribe digitalis to control the ventricular response rate in patients with HF and atrial fibrillation. *(Level of Evidence: A)*

2 It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias. *(Level of Evidence: C)*

Class IIb

1 The usefulness of current strategies to restore and maintain sinus rhythm in patients with HF and atrial fibrillation is not well established. *(Level of Evidence: C)*

2 The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. *(Level of Evidence: B)*

3 The benefit of enhancing erythropoiesis in patients with HF and anemia is not established. *(Level of Evidence: C)*

Class III

1 Class I or III antiarrhythmic drugs are not recommended in patients with HF for the prevention of ventricular arrhythmias. *(Level of Evidence: A)*

2 The use of antiarrhythmic medication is not indicated as primary treatment for asymptomatic ventricular arrhythmias or to improve survival in patients with HF. *(Level of Evidence: A)*

End-of-life considerations

Recommendations

Class I

1 Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended for patients with HF at the end of life. *(Level of Evidence: C)*

2 Patient and family education about options for formulating and implementing advance directives and the role of palliative and hospice care services with re-evaluation for changing clinical status is recommended for patients with HF at the end of life. *(Level of Evidence: C)*

3 Discussion is recommended regarding the option of inactivating ICDs for patients with HF at the end of life. *(Level of Evidence: C)*

4 It is important to ensure continuity of medical care between inpatient and outpatient settings for patients with HF at the end of life. *(Level of Evidence: C)*

5 Components of hospice care that are appropriate to the relief of suffering, including opiates, are recommended and do not preclude the options for use of inotropes and intravenous diuretics for symptom palliation for patients with HF at the end of life. *(Level of Evidence: C)*

6 All professionals working with HF patients should examine current end-of-life processes and work toward improvement in approaches to palliation and end-of-life care. *(Level of Evidence: C)*

Class III

Aggressive procedures performed within the final days of life (including intubation and implantation of a cardioverter-defibrillator in patients with NYHA functional class IV symptoms who are not anticipated to experience clinical improvement from available treatments) are not appropriate. *(Level of Evidence: C)*

Performance measures and standards

Simultaneous to the publication of the ACC/AHA Guidelines for the management of chronic heart failure, the ACC/AHA published a comprehensive set of performance measures for both the inpatient and outpatient care of heart failure patients [2]. Tables 13.4 and 13.5 outline the key recommendations. Likewise, a resource for data standards has also become available, so that common terminology in databases and registries might be attained [3].

A comparison of the ACC/AHA Guidelines with other recommendations

The recent proliferation of heart failure guidelines has prompted an inevitable comparison between the recommendations found in one set with that in another [4]. Table 13.6 depicts a brief comparison between recently published guidelines. Fortunately, some fundamental commonalities exist among the guidelines for low ejection fraction heart failure. These commonalities include a mandated trial of ACE inhibitors and beta-blockers for all patients; however, even this consensus is lessened somewhat by the details discussed in the individual guidelines with respect to issues such as which beta-blockers should be used or the symptomatic status of the patient with systolic dysfunction.

What are the reasons for the lack of uniformity between heart failure guidelines? Presumably, everyone has access to the same clinical trial publications. In a thoughtful editorial by McMurray and Swedberg, both of whom are prominent heart failure clinicians and trialists, several potential difficulties that face guideline writing committees were discussed. One major source of interpretive discrepancies is the increasing use of composite endpoints in heart failure trials. A new therapy, "Drug X," may reach a statistically significant outcome in a multicenter trial but only on the basis of a decrease in heart failure hospitalizations while no apparent effect on mortality is noted. Each guideline committee must then decide how to incorporate Drug X into its patient care recommendations.

Another source for the lack of uniformity between guidelines is the increasing complexity of a heart failure regimen upon which new therapies must be added. For example, several important trials have examined the morbidity and mortality effect of an additional investigational treatment onto a baseline regimen of diuretics, beta-blockers, and ACE-inhibitors in symptomatic patients. These trials have explored interventions with ARBs, aldosterone antagonists, implantable defibrillators (ICDs), cardiac resynchronization, and a specially

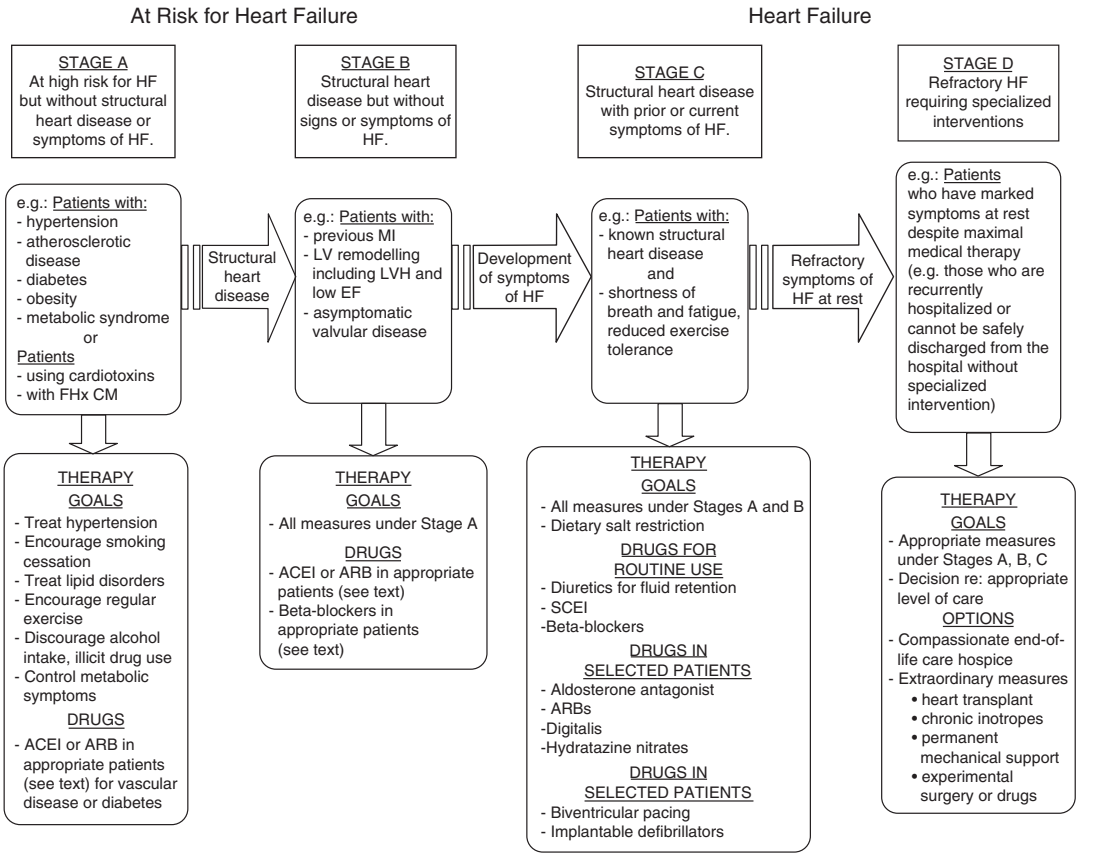

Fig. 13.1 Stages in the development of heart failure/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Table 13.5 Outpatient measure descriptions

Performance measure name	Measure description
1. Initial laboratory tests	Initial laboratory eveluation of patiens with newly diagnosed HF.
2. Left ventricular systolic (LVS) function assessment	Heart failure patients with documentation that LVS has been assessed.
3. Weight measurement	Measurement of patient's weight at each outpatient visit to assess change in volume status.
4. Blood pressure measurement	Measurement of patient's blood pressure at each outpatient visit.
5. Assessment of clinical symptoms of volume overload (excess)	Assessment of clinical symptoms of volume overload at each outpatient visit.
6. Assessment of clinical signs of volume overload (excess)	Completion of a physical examination pertaining to volume status assessment in patients diagnosed with HF at each outpatient visit.
7. Assessment of activity level	Evaluation of the impact of HF on activity level at each outpatient visit.
8. Patient education	Percentage of patients who were provided with patient education on disease management and health behavior changes during one or more visits within the period of assessment.
9. Beta-blocker therapy	Prescription of beta-blockers in patients with HF and left ventricular systolic dysfunction (LVSD).
10. ACE inhibitor or angiotensin receptor blocker (ARB) therapy for patients with heart failure who have left ventricular systolic dysfunction (LVSD)	Prescription of ACE inhibitor or ARB for management of outpatient HF patients with LVSD.
11. Warfarin therapy for patients with atrial fibrillation (AF)	Use of warfarin in patients with both HF and AF.

Table 13.6 Heart Failure Guidelines across societies

	ESC		ACC/AHA		CCS		HFSA	
	Level	**Class**	**Level**	**Class**	**Level**	**Class**	**Level**	**Class**
ACE – inhibitor	A	I	A	I	A	I	A	I
Beta-blocker	A	I	A	I	A	I	A	I
Aldosterone antagonists: moderate-severe symptoms/advanced HF	B	I	B	I	B	I	A	I
ARB								
ACE – inhibitor intolerant	B	I	A	I	A	I	A	I
ACE – inhibitor treated	–	–	B	IIb	A	I	A	IIa
To reduce mortality[a]	B	IIa	–	–	–	–	–	–
To reduce hospitalization[a]	A	I	–	–	–	–	–	–
Digoxin (sinus rhythm)	A	IIa	B	IIa	A	I	A[b]	IIa
Hydralazine – Isosorbide dinitrate								
ACE – inhibitor / ARB intolerant	B	IIa	C	IIb	B	IIb	C	IIa[d]
ACE – inhibitor – treated[e]	–	–	B	IIa	A	IIa	A[c]	I

[a] Only ESC guideline distinguishes between outcomes.

[b] NYHA classes II–III (level B in NYHA class IV).

[c] NYHA III or IV (level B in NYHA class II).

[d] IIa if intolerance because of renal insufficiency/hyperkalemia (otherwise ARB preferred and H-ISDN given a IIb recommendation).

[e] African-Americans.

After reference 3, with permission.

formulated hydralazine-nitrate combination. Nevertheless, no trials have addressed which of these successful interventions should be tried first for an individual patient who continues to be symptomatic despite optimal therapy. Guideline committees must then struggle to make reasonable interpretations of these data as they organize their reports. Are the outcomes of these trials valid for the current population of patients who may be on several additional drugs? Writing committees may consider these historical comparisons with widely divergent opinions.

Yet another area in which guideline writing committees disagree is their willingness to apply therapies to all heart failure patients which have only been studied in a specific subset of patients. Some examples of such dilemmas include the use of ICDs in patients who have never had heart failure symptoms, the use of spironolactone in asymptomatic patients, and the use of hydralazine-nitrates in patients other than African Americans. Achieving a consensus on these difficult items and scores of other equally contentious topics is unlikely.

Future directions

There is much to be done to improve the overall HF guideline development process. Future initiatives include:

1 A method to review and update the guidelines in a timely manner.
2 A method to simplify the guidelines so that they may be easily conveyed, and, most importantly, implemented.
3 Inclusion of recommendations for the management of acutely decompensated patients with HF.
4 Attempt to reconcile the differences between other organizations' guidelines.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book these relevant AHA statements and guidelines were published: Prevention of Heart Failure, http://circ.ahajournals.org/cgi/content/full/117/19/2544; Sleep Apnea and Cardiovascular Disease, http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.189420.

14 Cardiomyopathies

Barry J. Maron

Introduction
Definitions
Classification
Primary cardiomyopathies
Genetic
Hypertrophic cardiomyopathy (HCM)
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
Left ventricular noncompaction (LVNC)
Ion channelopathies
Mixed genetic and nongenetic
Dilated cardiomyopathy (DCM)
Primary restrictive (nonhypertrophied) cardiomyopathy
Acquired
Myocarditis (inflammatory cardiomyopathy)
Stress ("tako-tsubo") cardiomyopathy
Secondary cardiomyopathies
Recent ESC classification of cardiomyopathies

Introduction

Cardiomyopathies are an important and heterogeneous group of diseases for which awareness in both the public and medical communities has historically been impaired by persistent confusion surrounding definitions and nomenclature. Classification schemes, of which there have been many, are potentially useful in drawing relationships and distinctions between complex disease states for the purpose of promoting greater understanding, and indeed the precise language of these diseases is profoundly important.

Over the past decade with the dramatic advances in diagnosis, and understanding genetic and other etiologies, some definitions of diseases have become outdated. Indeed, several new myocardial disease entities have been identified and associated with rapid evolution of molecular genetics in cardiology, including the emergence of ion-channelopathies as diseases predisposing to primary lethal ventricular arrhythmias.

This expert consensus document, under the auspices of the American Heart Association (AHA) [1], constructs a contemporary classification of cardiomyopathies offering new perspectives to this complex and heterogeneous group of diseases, as well as clinical applications and implications for cardiac diagnosis. The classification scheme and disease definitions are designed to facilitate interaction among clinical and research communities in assessing the diagnosis, prognosis, and management of these diseases. However, as these new data continue to emerge, this classification will undoubtedly require further review and revision.

Definitions

The expert AHA consensus panel proposes this definition: *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/electrical dysfunction, and are due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.*

Within the broad definition, cardiomyopathies are usually associated with failure of myocardial

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performance, which may be mechanical (e.g., diastolic or systolic dysfunction) or as a primary electrical disease prone to life-threatening arrhythmias. Indeed, the ion channelopathies have been included within the present contemporary classification of primary cardiomyopathies based on the scientific assertion that ion channel mutations alter biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture.

Classification

See Fig. 14.1.

Cardiomyopathies are divided into two major groups based on predominant organ involvement: *Primary* cardiomyopathies (genetic, nongenetic, acquired) are those solely or predominantly confined to heart muscle, and are relatively few in number. *Secondary* cardiomyopathies show pathologic myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders. These systemic diseases associated with secondary forms of cardiomyopathies have previously been referred to as "specific cardiomyopathies" or "specific heart muscle diseases" in prior classifications, but that nomenclature has been abandoned here. The frequency and degree of secondary myocardial involvement varies considerably among these diseases, some of which are exceedingly uncommon, and the evidence of myocardial pathology may be sparse and reported in only a few patients. Since many cardiomyopathies predominantly involve the heart, but are not necessarily confined to that organ, some of the distinctions between primary and secondary cardiomyopathy are necessarily arbitrary, and inevitably rely on judgment concerning the clinical importance and consequences of the myocardial process.

Primary cardiomyopathies

Genetic

Hypertrophic cardiomyopathy (HCM)

HCM is a clinically heterogeneous but relatively common form of genetic heart disease transmitted as an autosomal dominant trait (1 : 500 of the general

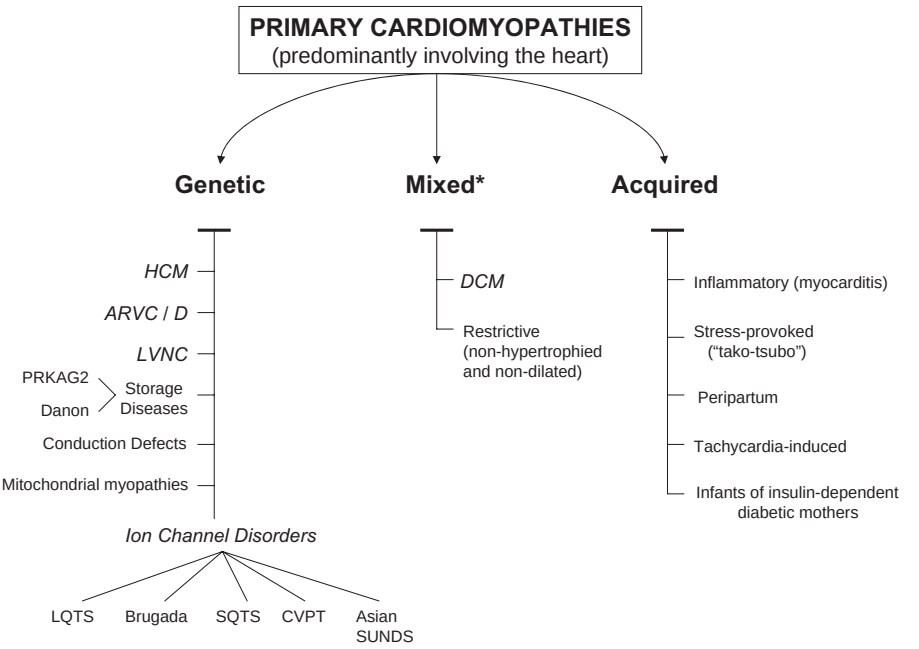

Fig. 14.1 Primary cardiomyopathies in which the clinically relevant disease processes are solely or predominantly confined to the working myocardium. The conditions have been segregated according to their known genetic or non-genetic etiologies. *At present, familial disease with a genetic etiology reported in a minority of cases.

population for the disease phenotype recognized by echocardiography), and probably the most frequently occurring cardiomyopathy. HCM is also the most common cause of sudden cardiac death in the young as well as in trained athletes (in the US) and is an important substrate for heart failure disability at any age.

HCM is characterized morphologically by virtue of an otherwise unexplained hypertrophied and nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of wall thickening evident (e.g., systemic hypertension, aortic valve stenosis), independent of whether obstruction to LV outflow is present. Clinical diagnosis is customarily made with two-dimensional echocardiography (or alternatively with cardiovascular magnetic resonance [CMR] imaging).

HCM demonstrates extreme genetic heterogeneity, and is caused by a variety of mutations encoding protein components of the cardiac sarcomere. Eleven mutated sarcomeric genes are presently associated with HCM, most commonly beta-myosin heavy chain (the first identified) and myosin-binding protein C. The other nine genes appear to account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin, α-tropomyosin, α-actin, α-myosin heavy chain, and muscle LIM protein (MLP). This intergenetic diversity displayed in HCM is compounded by considerable intra-genetic heterogeneity, with multiple mutations identified in each gene ($n = >400$ total individual mutations now). These are most commonly missense mutations altering only a single nucleotide (such as with beta-myosin heavy chain and α-tropomyosin), although other mutations cause protein truncation (e.g., myosin-binding protein C and troponin T). The characteristic diversity of the HCM phenotype is attributable to the disease-causing mutations, but probably also to the influence of modifier genes and environmental factors.

A number of other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring mostly in infants and children ≤4 years of age, which may resemble or mimic typical HCM due to sarcomere protein mutations. These cardiomyopathies also include secondary forms such as Noonan syndrome, an autosomal dominant cardiofacial condition associated with a variety of cardiac defects (most commonly, dysplastic pulmonary valve stenosis and atrial septal defect) due to mutations in PTPN11, a gene encoding the nonreceptor protein tyrosine phosphatase SHP-2 genes.

Other diseases in this category are mitochondrial myopathies due to mutations encoding mitochondrial DNA (including Kearns–Sayre syndrome), or mitochondrial proteins associated with ATP electron transport chain enzyme defects which alter mitochondrial morphology. Also included in these considerations are metabolic myopathies representing ATP production and utilization defects involving abnormalities of fatty acid oxidation (acyl CoA dehydrogenase deficiencies) and carnitine deficiency, as well as infiltrative myopathies – i.e., glycogen storage diseases (type II; autosomal recessive Pompe disease), Hunter's and Hurler's diseases, and also the transient and nonfamilial cardiomyopathy as part of generalized organomegaly, recognized in infants of insulin-dependent diabetic mothers. In older patients, a number of systemic diseases have been associated with hypertrophic forms of cardiomyopathy; these include Friedreich's ataxia, pheochromocytoma, neurofibromatosis, lentiginosis, and tuberous sclerosis.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)

ARVC/D is an uncommon form of inheritable heart muscle disease (estimated 1 : 5000), relatively recent in its description only about 20 years ago. It is mostly characterized by myocardial electrical instability and a risk for life-threatening ventricular arrhythmias. ARVC/D predominantly involves the right ventricle with progressive loss of myocytes and fibro-fatty tissue replacement, resulting in regional (segmental) or global abnormalities. Aneurysms of the right ventricle in the triangle of dysplasia (inflow, apex, outflow) are a specific feature. Apoptosis has been demonstrated as the mode for ongoing death of myocytes. Although frequently associated with myocarditis (enterovirus or adenovirus), ARVC/D is not considered a primary inflammatory cardiomyopathy. In addition, evidence of LV involvement with fibro-fatty replacement, chamber enlargement and myocarditis is also reported in up to 50–75% of patients.

In the majority of cases, ARVC/D shows autosomal dominant inheritance, albeit often with

incomplete penetrance. Dominant ARVC/D has been mapped to eight chromosomal loci, with mutations identified thus far in five genes. These include the cardiac ryanodine receptor RyR2, which is also responsible for familial catecholaminergic polymorphic ventricular tachycardia (CPVT); desmoplakin; plakophillin-2, desmoglein; as well as mutations altering regulatory sequences of the transforming growth factor-beta 3 gene. Two recessive forms have been described in conjunction with palmoplantar keratoderma and woolly hair (Naxos disease), and Carvajal syndrome, caused by mutations in junctional plakoglobin and desmoplakin, respectively. In terms of genomic background, ARVC/D may be considered a cell junction disease or a desmosomal cardiomyopathy. While the function of desmosomal proteins to anchor intermediate filaments to desmosomes implicates ARVC/D as a primary structural abnormality, there is also a link to ion-channel dysfunction.

Left ventricular noncompaction (LVNC)

Noncompaction of ventricular myocardium is a recently recognized congenital cardiomyopathy, characterized by a distinctive ("spongy") morphologic appearance of LV myocardium. Noncompaction predominantly involves the distal (apical) portion of the LV chamber with deep intertrabecular recesses (sinusoids) in communication with the ventricular cavity, resulting from an arrest in normal embryogenesis. LVNC may be an isolated finding or associated with other congenital heart anomalies such as complex cyanotic congenital heart disease.

Ion channelopathies

There is a growing list of uncommon inherited and congenital arrhythmia disorders caused by mutations in genes that encode defective ionic channel proteins (which govern cell and sarcoplasmic reticulum membrane transit of sodium, potassium and calcium ions). These ion channel disorders include long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Sudden unexplained nocturnal death syndrome (SUNDS) in young Southeast Asian males and Brugada syndrome are based on a similar clinical and genetic profile. A small proportion (5–10%) of sudden infant deaths may also be linked to ion channelopathies, including LQTS, SQTS, CPVT and Brugada syndrome. Clinical diagnosis of the ion channelopathies can often be made by identification of the disease phenotype on standard 12-lead ECG.

LQTS is probably the most common of the ion channelopathies, characterized by prolongation of ventricular repolarization and QT interval (corrected for heart rate) on the standard 12-lead ECG, a specific form of polymorphic ventricular tachycardia (Torsade des pointes), and a risk for syncope and sudden cardiac death. Phenotypic expression (on the ECG) varies considerably and about 25–50% of genetically affected family members may show borderline or even normal QT intervals.

Two patterns of inheritance have been described in LQTS: (1) a rare autosomal recessive disease associated with deafness (Jervell and Lange Nielsen syndrome), and caused by two genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1 [minK]); and (2) the much more common autosomal dominant disease unassociated with deafness (Romano–Ward syndrome), which is caused by mutations in eight different genes. These include: KCNQ1 (KvLQT1; LQT1); KCNH2 (HERG; LQT2); SCN5A (Na1.5; LQT3); ANKB (LQT4); KCNE1 (minK; LQT5); KCNE2 (MiRP1; LQT6); KCNJ2 (Kir2.1; LQT7; Andersen's syndrome) and CACNA1C (Ca1.2; LQT8; Timothy syndrome). Of the eight genes, six encode for cardiac potassium channels, one for the sodium channel (SCN5A; LQT3) and one for the protein ankyrin, which is involved in anchoring ion channels to the cellular membrane (ANKB).

Brugada syndrome is a relatively new clinical entity associated with sudden cardiac death in young people. First described in 1992, the syndrome is identified by a distinctive ECG pattern consisting of right bundle branch block and coved ST-segment elevation in the anterior precordial leads (V1–V3). The characteristic ECG pattern is often concealed and may be unmasked with the administration of sodium channel blockers, including ajmaline, flecainide, procainamide or pilsicainide. Familial autosomal dominant and sporadic forms have been linked to mutations in an α-subunit of the cardiac sodium channel gene SCN5A (the same gene responsible for LQT3) in 20% of patients with the Brugada syndrome. Another locus has been reported on the

short arm of chromosome 3, but no gene has yet been identified.

SUNDS, found predominantly in young Southeast Asian males (i.e., Thailand, Japan, Philippines and Cambodia), is a disorder causing sudden death during sleep due to ventricular tachycardia/fibrillation. Some cases of SUNDS due to SCN5A gene mutations and Brugada syndrome have been shown to be phenotypically, genetically, and functionally the same disorder.

CPVT, a disease first described by Coumel and co-workers in 1978, is characterized by syncope, sudden death and polymorphic ventricular tachycardia triggered by vigorous physical exertion or acute emotion (usually in children and adolescents), a normal resting ECG and the absence of structural cardiac disease. Family history of one or multiple sudden cardiac deaths is evident in 30% of cases. The resting ECG is unremarkable with the exception of sinus bradycardia and prominent U-waves in some patients. The autosomal dominant form of the disease has been linked to the RyR2 gene encoding for the cardiac ryanodine receptor, a large protein that forms the calcium release channel in the sarcoplasmic reticulum and is essential for regulation of excitation-contraction coupling and intracellular calcium levels.

Short QT syndrome (SQTS), first described in 2000, is characterized by short QT interval (<330 msec) on ECG and a high incidence of sudden cardiac death due to VT/VF. Another distinctive ECG feature of SQTS is the appearance of tall peaked T waves, similar to those encountered with hyperkalemia. The syndrome has been linked to gain of function mutations in KCNH2 (HERG; SQT1); KCNQ1 (KvLQT1; SQT2); and KCNJ2 (Kir2.1; SQT3), causing an increase in the intensity of IKr, Iks, and Ikl, respectively.

Mixed genetic and nongenetic

Dilated cardiomyopathy (DCM)

Dilated forms of cardiomyopathy are characterized by ventricular chamber enlargement and systolic dysfunction, with normal LV wall thickness; diagnosis is usually made with two-dimensional echocardiography. DCM leads to progressive heart failure and decline in LV contractile function, ventricular and supraventricular arrhythmias, conduction system abnormalities, thromboembolism and sudden or heart failure-related death. Indeed, DCM is a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2500 people and is the third most common cause of heart failure and the most frequent indication of heart transplantation.

The DCM phenotype with sporadic occurrence may be derived from a particularly broad range of primary (and secondary) etiologies including: infectious agents, particularly viruses, often producing myocarditis [cardiotropic virus like coxsackie, adenovirus, parvovirus, HIV); but also bacterial; fungal rickettsial; myobacterial; parasitic (e.g., Chagas disease due to trypanosome cruzi infection).

Other causes include toxins, chronic excessive consumption of alcohol, chemotherapeutic agents (anthracyclines such as doxorubicin and daunorubicin); metals and other compounds (cobalt, lead, mercury and arsenic); autoimmune and systemic disorders (including collagen vascular disorders); pheochromocytoma, neuromuscular disorders such as Duchenne/Becker and Emery–Dreifuss muscular dystrophies; mitochondrial; metabolic; endocrine; and nutritional disorders (e.g., carnitine, selenium deficiencies). In addition, a substantial proportion of cases aggregate in families, or remain designated as idiopathic.

About 20–35% of DCM cases have been reported as familial, although with incomplete and age dependent penetrance, and linked to a diverse group of more than 20 loci and genes. While genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance less frequent. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins which are responsible for HCM, including α-cardiac actin, α-tropomyosin, cardiac troponin T, I and C, beta and alpha-myosin heavy chain, myosin binding protein C, Z-disc protein-encoding genes including muscle LIM protein (MLP), α-actinin-2, ZASP and titin have also been identified.

DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcolemmal, nuclear envelope, sarcomere and transcriptional coactivator proteins. The most common of these is probably the lamin A/C gene, also associated with conduction system disease, which encodes a nuclear

envelope intermediate filament protein. Mutations in this gene also cause Emery–Dreifuss muscular dystrophy (EDMD). The X-linked gene responsible for EDMD, emerin (another nuclear lamin protein) also causes similar clinical cardiac features. Other DCM genes of this type include desmin, caveolin, and α- and β.b-sarcoglycan as well as the mitochondrial respiratory chain gene. X-linked DCM (XLCM) is caused by the Duchenne muscular dystrophy (dystrophin) gene, while G 4.5 (tafazzin) – a mitochondrial protein of unknown function – causes Barth syndrome, an X-linked cardioskeletal myopathy in infants.

Primary restrictive (nonhypertrophied) cardiomyopathy

Primary restrictive cardiomyopathy as defined here is a rare form of nonhypertrophied, nondilated heart muscle disease and a cause of heart failure. It is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal LV wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function. Both sporadic and familial forms have been described and in one family a troponin I mutation was responsible for both restrictive cardiomyopathy and HCM.

Acquired

Myocarditis (inflammatory cardiomyopathy)

Myocarditis, an acute or chronic inflammatory process affecting the myocardium, is produced by a wide variety of toxins and drugs (e.g., cocaine, interleukin 2) or infectious agents – most commonly including viral (e.g., coxsackie, adenovirus, parvovirus HIV); bacterial (e.g., diphtheria, meningococcus, psittacosis, streptococcus); rickettsial (e.g., typhus; Rocky Mountain spotted fever); fungal (e.g., aspergillosus, candidiasis); and parasitic (Chagas disease, toxoplasmosis), as well as Whipple disease (intestinal lipodystrophy), immune (giant cell myocarditis) and hypersensitivity reactions to drugs such as antibiotics, sulfonamides, anti-convulsants and anti-inflammatories. Endocardial fibroelastosis is a dilated cardiomyopathy in infants and children, as a consequence of viral myocarditis in utero (mumps) which has become quite rare.

Table 14.1 Secondary cardiomyopathies

Infiltrative†
- Amyloidosis (primary [AL]; familial autosomal dominant [AF]*; senile [SSA]; secondary [AA] forms)
- Gaucher disease*
- Hurler's disease*
- Hunter's disease*

Storage‡
- Hemochromatosis
- Fabry's disease*
- Glycogen storage disease* (type II; Pompe's)
- Nieman-Pick disease*

Toxicity
- Drugs; heavy metals; chemical agents

Endomyocardial
- Endomyocardial fibrosis (EMF)
- Hypereosinophilic syndrome (Loeffler's endocarditis)

Inflammatory (granulomatous)
- Sarcoidosis

Endocrine
- Diabetes mellitus*
- Hyperthyroidism
- Hypothyroidism
- Hyperparathyroidism
- Pheochromocytoma
- Acromegaly

Cardiofacial
- Noonan's syndrome*
- Lentiginosis*

Neuromuscular/neurologic
- Friedreich's ataxia*
- Duchenne–Becker muscular dystrophy*
- Emery–Dreifuss muscular dystrophy (EDMD)*
- Myotonic dystrophy*
- Neurofibromatosis*
- Tuberous sclerosis*

Nutritional deficiencies
- Beriberi (thiamine); pellagra; scurvy; selenium; carnitine; kwashiorkor

Autoimmune/collagen
- Systemic lupus erythematosis
- Dermatomyositis
- Rheumatoid arthritis
- Scleroderma
- Polyarteritis nodosa

Electrolyte imbalance

Consequence of cancer therapy
- Anthracyclines: doxorubicin (adriamycin), daunorubicin
- Cyclophosphamide
- Radiation

* Genetic (familial) etiology.

† Accumulation of abnormal substances *between* myocytes (i.e., extracellular).

‡ Accumulation of abnormal substances *within* myocytes (i.e., intracellular).

Myocarditis typically evolves through active, healing and healed stages, characterized progressively by inflammatory cell infiltrates leading to interstitial edema and focal myocyte necrosis and ultimately replacement fibrosis. These pathologic processes create an electrically unstable substrate potentially predisposing to the development of ventricular tachyarrhythmias and even sudden death. In some instances, an episode of viral myocarditis (frequently subclinical) can trigger an autoimmune reaction that causes immunologic damage to the myocardium or cytoskeletal disruption, culminating in DCM with LV dysfunction.

Stress ("tako-tsubo") cardiomyopathy

Stress cardiomyopathy, first reported in Japan as "tako-tsubo," is a recently described clinical entity characterized by acute, but rapidly reversible LV systolic dysfunction in the absence of atherosclerotic coronary artery disease, and triggered by profound psychological stress. This distinctive form of ventricular stunning typically affects older women and preferentially involves the distal portion of the LV chamber ("apical ballooning"), with basal hypercontractility. Although presentation often mimics ST-segment elevation myocardial infarction, outcome is favorable with appropriate medical therapy.

Secondary cardiomyopathies

The most important secondary cardiomyopathies are provided in Table 14.1. This list is not, however, intended to represent an exhaustive and complete tabulation of the vast number of systemic conditions reported to involve the myocardium, but rather is limited to the most common of these diseases frequently associated with a cardiomyopathy.

Recent ESC classification of cardiomyopathies

Another classification of cardiomyopathies has recently been promoted under the auspices of the European Society of Cardiomyopathy and European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases, apparently in response to the AHA classification [2] (Fig. 14.2). The ESC document is designed based on the premise that contemporary understanding of the cardiomyopathies is only confused by genetic diagnostic "labels." The ESC working group segregates diseases based on "specific morphological and functional phenotypes," in effect expanding the 1995 World Health Organization Classification scheme [3], while abandoning the distinction between primary and secondary cardiomyopathies used by AHA.

Consequently, the ESC classification is advanced by the authors as (in some undefined way) more effective for routine clinical practice. In contrast, the AHA document is criticized by ESC as most suited for research purposes. However, this latter characterization would not seem to be justified, given the similarities of the two documents with respect to clinical diagnostic definitions, and even the classifi-

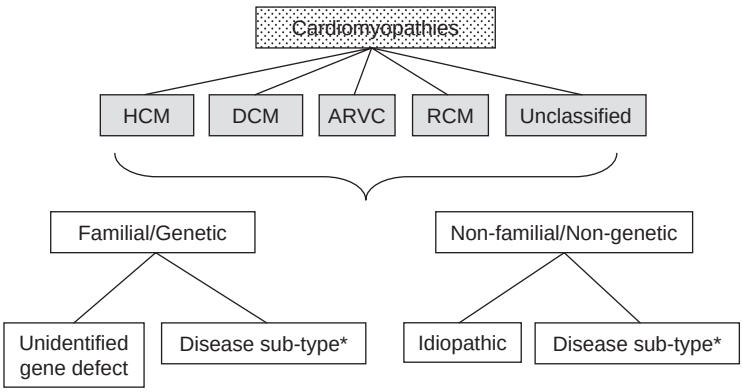

Fig. 14.2 Summary of proposed ESC cardiomyopathy classification system. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

cation itself which ultimately separates disease states into familial and nonfamilial categories (rather than genetic and nongenetic, as in the AHA classification). Nevertheless, considering the complex nature of the cardiomyopathies, and the shortcomings implicit in all attempts at their classification, there is probably no definitive construct that is likely to satisfy the purposes of all interested parties and disciplines in this regard.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

15 Atrial Fibrillation

Valentin Fuster and Lars Rydén

Organization of committee and evidence
Review
Changes since the initial publication of the 2001 guidelines
Recommendations for management of patients with atrial fibrillation
Pharmacological rate control during atrial fibrillation
Preventing thromboembolism
Cardioversion of atrial fibrillation
Pharmacological cardioversion
Direct-current cardioversion
Pharmacological enhancement of direct-current cardioversion
Prevention of thromboembolism in patients with atrial fibrillation undergoing cardioversion
Maintenance of sinus rhythm
Future directions
Novel antithrombotic compounds
Ablation strategies

Organization of committee and evidence

Review

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease [1,2]. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and cost [3,4]. Accordingly, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) created a committee, composed of representatives of the ACC, AHA, ESC, the European Heart Rhythm Association (EHRA), and the Heart Rhythm Society (HRS), to establish guidelines for optimum management of this frequent and complex arrhythmia. The first version of these guidelines was released in 2001. The ACC/AHA/ESC Writing Committee to revise the 2001 Guidelines conducted a comprehensive review of the relevant literature from 2001 to 2006 using the PubMed/MEDLINE and Cochrane Library databases [1].

Changes since the initial publication of the 2001 guidelines

Besides incorporating major clinical trials such as those that compared rhythm control and rate control approaches to long-term management the text was reorganized to better reflect implications for patient care. Presently it starts with recognition of AF and its pathogenesis and the general priorities of rate control, prevention of thromboembolism, and methods available for use in selected patients to correct the arrhythmia and maintain normal sinus rhythm. Advances in catheter-based ablation technologies have been incorporated. Recommendations do, however, recognize that such vital details as patient selection, optimum catheter positioning, absolute rates of treatment success, and the frequency of complications remain incompletely evaluated in prospective, randomised trials. Sections on drug therapy have been confined to human studies with compounds approved for clinical use in North America and/or Europe. As data on the management of patients prone to AF in special circumstances are more robust, recommendations are based on a higher level of evidence than in the first

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edition. Efforts were made to maintain consistency with other ACC/AHA and ESC practice guidelines.

Recommendations for management of patients with atrial fibrillation

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA/ESC format as described in the table in the front of the book. The reader is referred to the full-text guidelines for a complete description of the rationale and evidence supporting these recommendations.

Pharmacological rate control during atrial fibrillation

Class I

1 Measurement of the heart rate at rest and control of the rate using pharmacological agents (either a beta-blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF (Fig. 15.1). *(Level of Evidence: B)*

2 In the absence of preexcitation, intravenous administration of beta-blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or heart failure (HF). *(Level of Evidence: B)*

3 Intravenous administration of digoxin or amiodarone is recommended to control the heart rate in patients with AF and HF who do not have an accessory pathway. *(Level of Evidence: B)*

4 In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacological treatment as necessary to keep the rate in the physiological range. *(Level of Evidence: C)*

5 Digoxin is effective following oral administration to control the heart rate at rest in patients with AF and is indicated for patients with HF, left ventricular (LV) dysfunction, or for sedentary individuals. *(Level of Evidence: C)*

Class IIa

1 A combination of digoxin and either a beta-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia. *(Level of Evidence: B)*

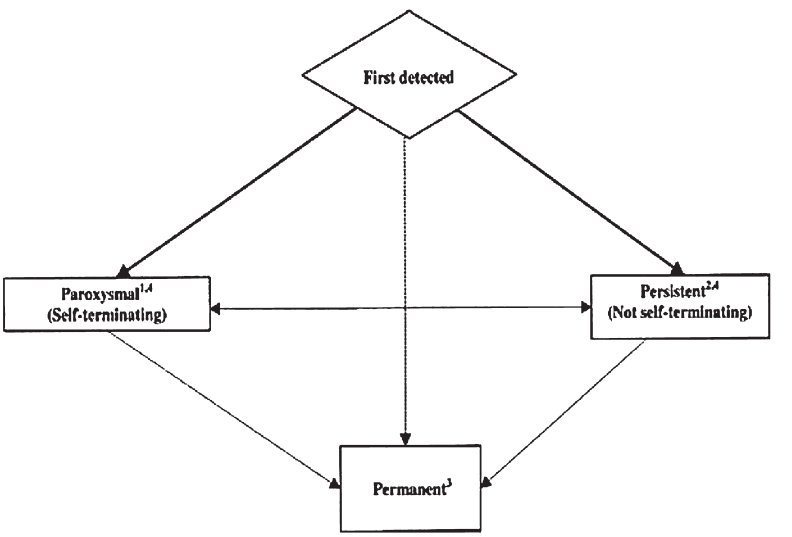

Fig. 15.1 Patterns of atrial fibrillation (AF). 1. Episodes that generally last 7 days or less (most less than 24 hours); 2. episodes that usually last more than 7 days; 3. cardioversion failed or not attempted; and 4. both paroxysmal and persistent AF may be recurrent.

2 It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacological therapy is insufficient or associated with side effects. *(Level of Evidence: B)*

3 Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated. *(Level of Evidence: C)*

4 When electrical cardioversion is not necessary in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative. *(Level of Evidence: C)*

Class IIb

1 When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a beta-blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate. *(Level of Evidence: C)*

2 Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway. *(Level of Evidence: B)*

3 When the rate cannot be controlled with pharmacological agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate. *(Level of Evidence: C)*

Class III

1 Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF. *(Level of Evidence: B)*

2 Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF. *(Level of Evidence: C)*

3 In patients with decompensated HF and AF, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended. *(Level of Evidence: C)*

4 Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended [6–10]. *(Level of Evidence: C)*

Preventing thromboembolism

Class I

1 Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications. *(Level of Evidence: A)*

2 The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient (Fig. 15.2) [11,12]. *(Level of Evidence: A)*

3 For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity international normalized ratio (INR) of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, transient ischemic attack [TIA], or systemic embolism) and rheumatic mitral stenosis. *(Level of Evidence: A)*

4 Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. Such factors include age 75 years or greater, hypertension, HF, impaired LV systolic function (ejection fraction 35% or less or fractional shortening less than 25%), and diabetes mellitus (Fig. 15.3, Fig. 15.4) [13,14]. *(Level of Evidence: A)*

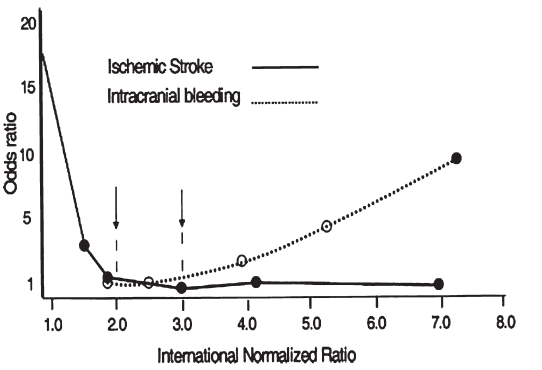

Fig. 15.2 Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from [11]. Data from [12].

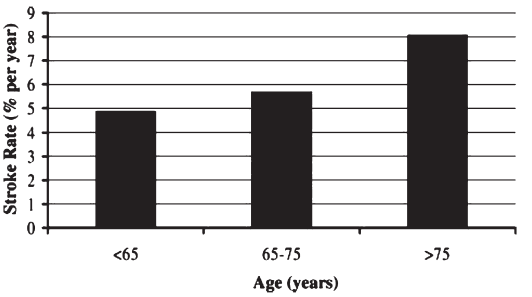

Fig. 15.3 Stroke rates in relation to age among patients in untreated control groups of randomized trials of antithrombotic therapy. Data from [13].

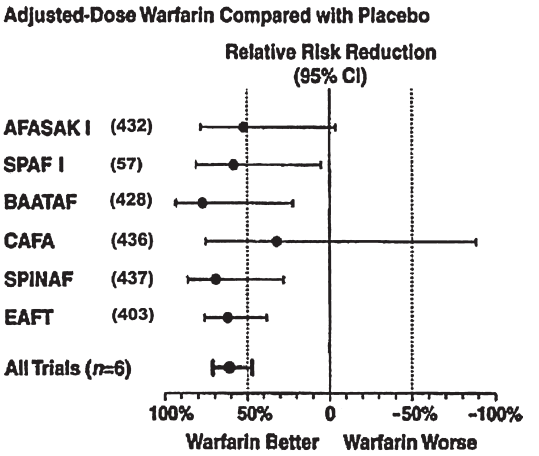

Fig. 15.4 Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation. Adjusted-dose warfarin compared with placebo (six random trials). AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. Modified with permission from [14].

5 INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. *(Level of Evidence: A)*

6 Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation (Fig. 15.5) [14]. *(Level of Evidence: A)*

7 For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5. *(Level of Evidence: B)*

8 Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. *(Level of Evidence: C)*

Class IIa

1 For primary prevention of thromboembolism in patients with nonvalvular AF who have just one of the following validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences: age greater than or equal to 75 years (especially in female patients), hypertension, HF, impaired LV function, or diabetes mellitus. *(Level of Evidence: A)*

2 For patients with nonvalvular AF who have one or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 years, female gender, or CAD. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences. *(Level of Evidence: B)*

3 It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF. *(Level of Evidence: B)*

4 In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 week without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding. *(Level of Evidence: C)*

5 It is reasonable to reevaluate the need for anticoagulation at regular intervals. *(Level of Evidence: C)*

Class IIb

1 In patients 75 years of age and older at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism

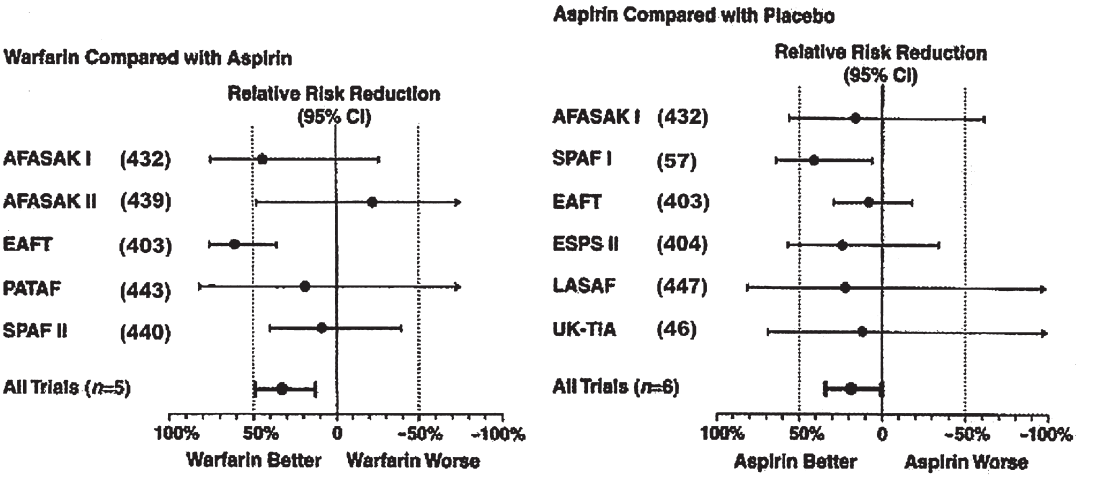

Fig. 15.5 Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular atrial fibrillation: warfarin compared with aspirin and aspirin compared with placebo. AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, United Kingdom Transient Ischaemic Attack Aspirin Trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. Modified with permission from [14].

who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0 to 3.0, a lower INR target of 2.0 (range 1.6 to 2.5) may be considered for primary prevention of ischemic stroke and systemic embolism. *(Level of Evidence: C)*

2 When surgical procedures require interruption of oral anticoagulant therapy for longer than 1 week in high-risk patients, unfractionated heparin may be administered or low-molecular-weight heparin given by subcutaneous injection, although the efficacy of these alternatives in this situation is uncertain. *(Level of Evidence: C)*

3 Following percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (less than 100 mg per day) and/or clopidogrel (75 mg per day) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. *(Level of Evidence: C)*

4 In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0). Clopidogrel should be given for a minimum of 1 month after implantation of a bare metal stent, at least 3 months for a sirolimus-eluting stent, at least 6 months for a paclitaxel-eluting stent, and 12 months or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated. *(Level of Evidence: C)*

5 In patients with AF younger than 60 years without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established. *(Level of Evidence: C)*

6 In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity anticoagulation (INR 2.0 to 3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of the anticoagulation to a

maximum target INR of 3.0 to 3.5. *(Level of Evidence: C)*

Class III

Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 years without heart disease (lone AF) or any risk factors for thromboembolism [14]. *(Level of Evidence: C)*

Cardioversion of atrial fibrillation

Pharmacological cardioversion

Class I

Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF (Figs 15.6, Fig. 15.7). *(Level of Evidence: A)*

Class IIa

1 Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF. *(Level of Evidence: A)*

2 A single oral bolus dose of propafenone or flecainide ("pill-in-the-pocket") can be administered to terminate persistent AF outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta-blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. *(Level of Evidence: C)*

3 Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary. *(Level of Evidence: C)*

Class IIb

Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. *(Level of Evidence: C)*

Class III

1 Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. *(Level of Evidence: A)*

2 Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm. *(Level of Evidence: B)*

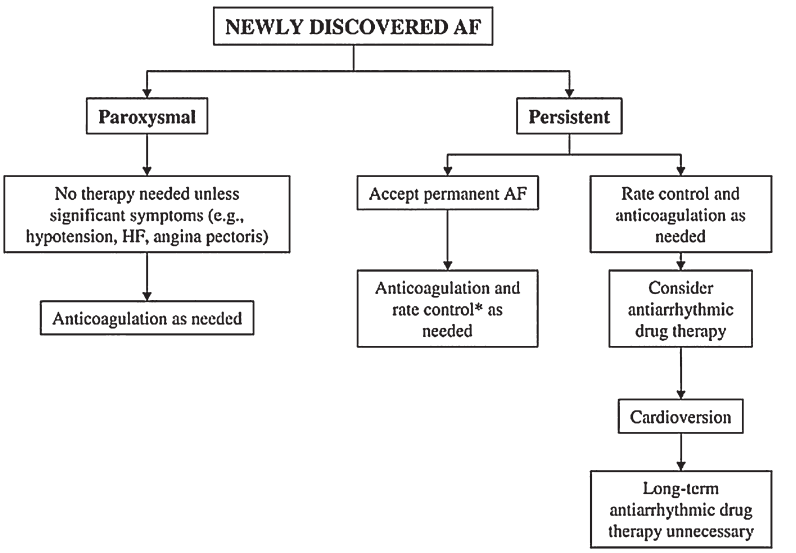

Fig. 15.6 Pharmacological management of patients with newly discovered atrial fibrillation (AF). See Fig. 15.9. HF indicates heart failure.

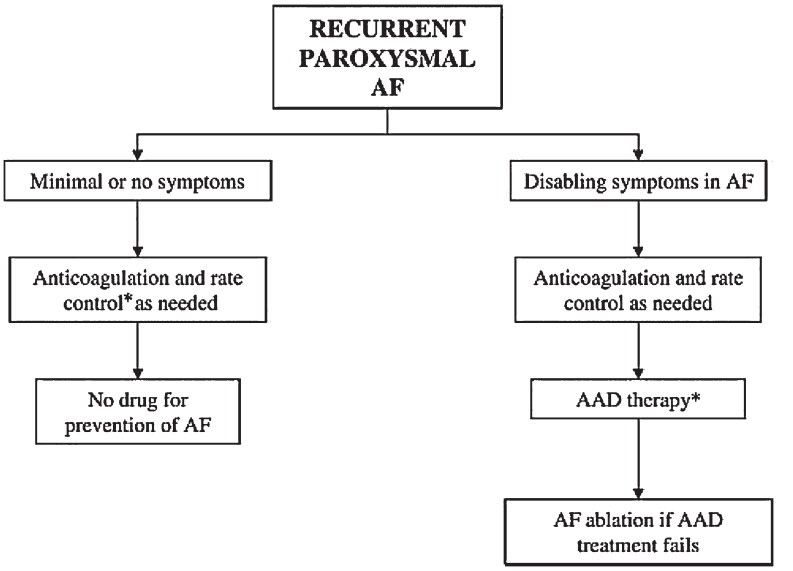

Fig. 15.7 Pharmacological management of patients with recurrent paroxysmal atrial fibrillation (AF).
*See Fig. 15.9. AAD indicates antiarrhythmic drug.

Direct-current cardioversion

Class I

1 When a rapid ventricular response does not respond promptly to pharmacological measures for patients with AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or HF, immediate R-wave synchronized direct-current cardioversion is recommended. *(Level of Evidence: C)*

2 Immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs. *(Level of Evidence: B)*

3 Cardioversion is recommended in patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after cardioversion, repeated direct-current cardioversion attempts may be made following administration of antiarrhythmic medication. *(Level of Evidence: C)*

Class IIa

1 Direct-current cardioversion can be useful to restore sinus rhythm as part of a long-term management strategy for patients with AF. *(Level of Evidence: B)*

2 Patient preference is a reasonable consideration in the selection of infrequently repeated cardioversions for the management of symptomatic or recurrent AF. *(Level of Evidence: C)*

Class III

1 Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple cardioversion procedures despite prophylactic antiarrhythmic drug therapy. *(Level of Evidence: C)*

2 Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia. *(Level of Evidence: C)*

Pharmacological enhancement of direct-current cardioversion

Class IIa

1 Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent AF. *(Level of Evidence: B)*

2 In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure following prophylactic administration of antiarrhythmic medication. *(Level of Evidence: C)*

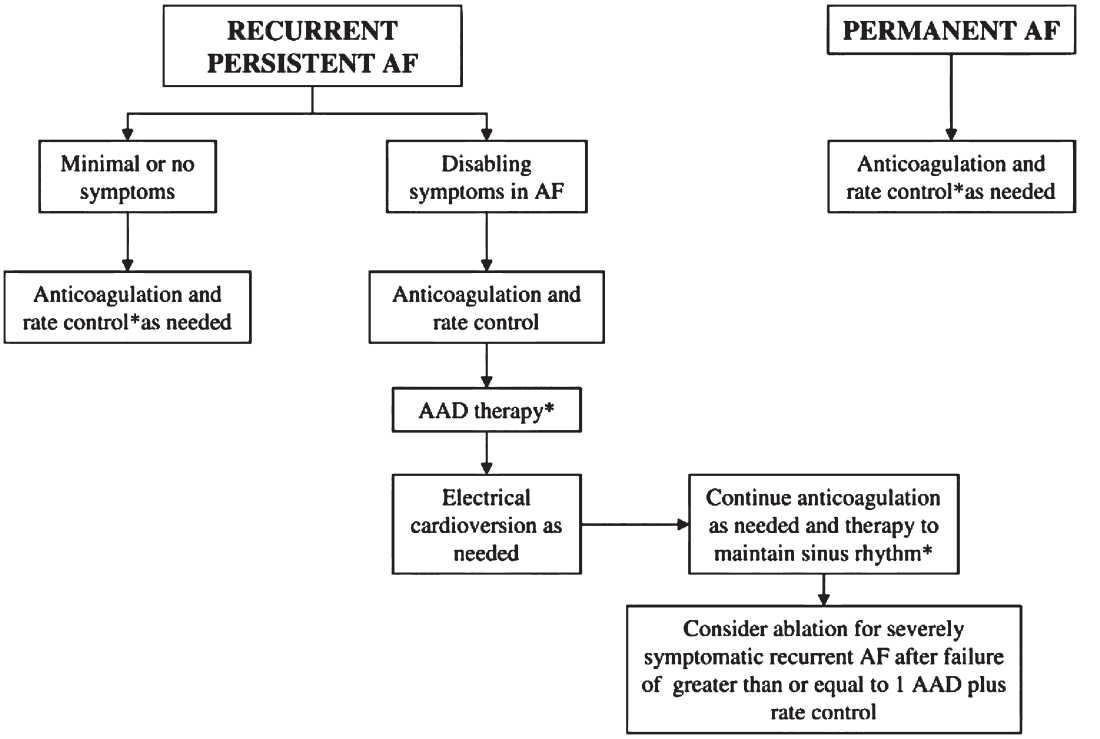

Fig. 15.8 Pharmacological management of patients with recurrent persistent or permanent atrial fibrillation (AF).
*See Fig. 15.9. Initiate drug therapy before cardioversion to reduce the likelihood of early recurrence of AF. AAD indicates antiarrhythmic drug.

Class IIb

1 For patients with persistent AF, administration of beta-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain (Fig. 15.8). *(Level of Evidence: C)*

2 Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF. *(Level of Evidence: C)*

3 Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient [15–21]. *(Level of Evidence: C)*

Prevention of thromboembolism in patients with atrial fibrillation undergoing cardioversion

Class I

1 For patients with AF of 48-h duration or longer, or when the duration of AF is unknown, anticoagulation (INR 2.0 to 3.0) is recommended for at least 3 weeks prior to and 4 weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. *(Level of Evidence: B)*

2 For patients with AF of more than 48-h duration requiring immediate cardioversion because of hemodynamic instability, heparin should be administered concurrently (unless contraindicated) by an initial intravenous bolus injection followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the reference control value. Thereafter, oral anticoagulation (INR 2.0 to 3.0) should be provided for at least 4 weeks, as for patients undergoing elective cardioversion. Limited data support subcutaneous administration of low-molecular-weight heparin in this indication. *(Level of Evidence: C)*

3 For patients with AF of less than 48-h duration associated with hemodynamic instability (angina pectoris, myocardial infarction [MI], shock, or pulmonary edema), cardioversion should be performed

immediately without delay for prior initiation of anticoagulation. *(Level of Evidence: C)*

Class IIa

1 During the 48 h after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism. *(Level of Evidence: C)*

2 As an alternative to anticoagulation prior to cardioversion of AF, it is reasonable to perform transesophageal echocardiography (TEE) in search of thrombus in the left atrium (LA) or left atrial appendage (LAA). *(Level of Evidence: B)*

2(a) For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (e.g., initiated by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2 times the control value until oral anticoagulation has been established with an oral vitamin K antagonist (e.g., warfarin) as evidenced by an INR equal to or greater than 2.0). *(Level of Evidence: B)* Thereafter, continuation of oral anticoagulation (INR 2.0 to 3.0) is reasonable for a total anticoagulation period of at least 4 wk, as for patients undergoing elective cardioversion. *(Level of Evidence: B)* Limited data are available to support the subcutaneous administration of a low-molecular-weight heparin in this indication. *(Level of Evidence: C)*

2(b) For patients in whom thrombus is identified by TEE, oral anticoagulation (INR 2.0 to 3.0) is reasonable for at least 3 weeks prior to and 4 weeks after restoration of sinus rhythm, and a longer period of anticoagulation may be appropriate even after apparently successful cardioversion, because the risk of thromboembolism often remains elevated in such cases. *(Level of Evidence: C)*

3 For patients with atrial flutter undergoing cardioversion, anticoagulation can be beneficial according to the recommendations as for patients with AF [22–24]. *(Level of Evidence: C)*

Maintenance of sinus rhythm

See Fig. 15.9.

Class I

Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. *(Level of Evidence: C)*

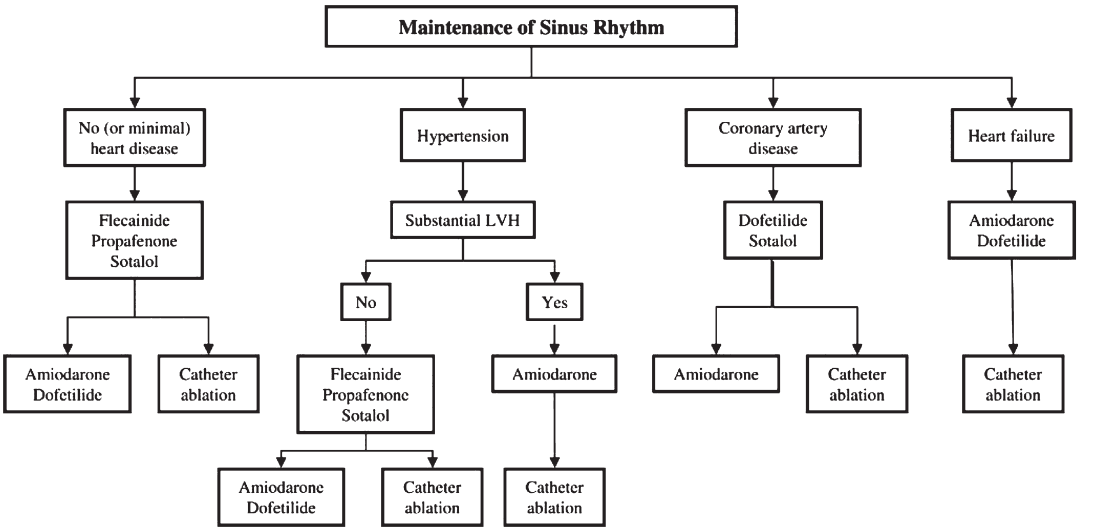

Fig. 15.9 Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy.

Class IIa

1 Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. *(Level of Evidence: C)*

2 Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. *(Level of Evidence: C)*

3 Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. *(Level of Evidence: C)*

4 In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. *(Level of Evidence: B)*

5 Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with Class III drug-related proarrhythmia are not present. *(Level of Evidence: C)*

6 Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement (Fig. 15.10). *(Level of Evidence: C)*

Class III

1 Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. *(Level of Evidence: A)*

2 Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or atrioventricular (AV) node dysfunction unless they have a functioning electronic cardiac pacemaker [25–27]. *(Level of Evidence: C)*

Future directions

Two presently promising areas of development involve alternative oral anticoagulation strategies and various ablation techniques.

Novel antithrombotic compounds

Several antithrombotic compounds are in different stages of development combining the goals of simplifying administration and monitoring compared to the use of warfarin. Ideally they will cause fewer bleeding complications and still provide adequate thromboembolic protection.

Ximelagatran, an oral direct thrombin (factor IIa) inhibitor administered in a fixed dose without need for monitoring of anticoagulation intensity, would have been an ideal replacement for warfarin. Unfortunately the phase III double-blinded study, SPORTIF V (Stroke Prevention with the Oral Direct

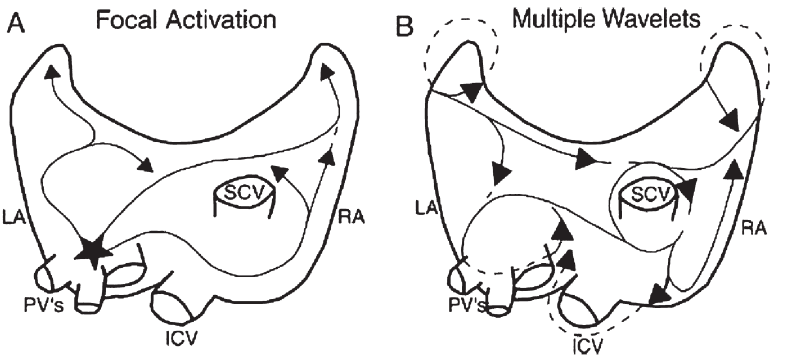

Fig. 15.10 Posterior view of principal electrophysiological mechanisms of atrial fibrillation. **A**, Focal activation. The initiating focus (indicated by the star) often lies within the region of the pulmonary veins. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. **B**, Multiple-wavelet reentry. Wavelets (indicated by arrows) randomly re-enter tissue previously activated by the same or another wavelet. The routes the wavelets travel vary. LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium. Reproduced with permission from [25].

Thrombin Inhibitor Ximelagatran), revealed a 6.0% incidence of liver transaminase abnormality above three times normal values and 1–2 deaths from liver disease. The primary end-point of all strokes (ischemic or hemorrhagic) and systemic embolism was reached in 1.6% of patients on ximelagatran and 1.2% of patients on warfarin. Although promising, the FDA denied approval in 2004. Despite the failure of ximelagatran, there are several promising drugs in the mid to late phases of development. Dabigatran etexilate, another oral direct thrombin inhibitor, is examined in the phase III RELY trial (Randomized Evaluation of Long Term Anticoagulant Therapy), comparing two different fixed doses versus dose-adjusted warfarin. RELY is expected to be completed in 2009.

Factor Xa is another therapeutic target for inhibition that has large bodies of evidence supporting its efficacy for treatment and prevention of thromboembolism. Until recently, factor Xa inhibitors required injection, but several oral compounds are presently undergoing phase II and III investigation. A phase III trial of Rivaroxaban comparing its efficacy to dose adjusted warfarin for the prevention of stroke in atrial fibrillation is enrolling patients. Another, apixaban, is in a similar stage of development. It is likely that some of these compounds will provide viable alternatives to warfarin for patients at moderate to high risk for stroke while low risk patients still will be well served by aspirin.

Ablation strategies

Many trials involving ablation strategies for atrial fibrillation are under way, and an important pharmacological trial on dronedarone has just been published [28]. They are expected to help answer which ablation techniques that are to be preferred in maintaining sinus rhythm. The trials compare complete versus incomplete electrical isolation of the pulmonary veins (German Atrial Fibrillation Network) and trigger-based ablation techniques (pulmonary vein isolation) versus substrate-based ablation techniques guided by high-frequency, fractionated electrograms (University of Toronto). MANTRA-PF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) and RAAFT (First Line Radiofrequency Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment) are both prospective, randomized, multi-center studies comparing pharmacologic anti-arrhythmic therapy to pulmonary vein isolation. Expected enrollment is 300 and 400 patients respectively with expected completion of 2009 or later. CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) has as its primary objective to determine if the effects of the strategy catheter ablation of AF is superior to optimized conventional pharmacological therapy on Quality of Life in patients with symptomatic AF.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: ACC/AHA/Physician Consortium 2008 Clinical Performance Measures for Adults With Nonvalvular Atrial Fibrillation or Atrial Flutter, http://circ.ahajournals.org/cgi/content/full/117/8/1101.

16 Supraventricular Arrhythmias

Carina Blomström-Lundqvist and Melvin Scheinman

Organization of committee and evidence review
General evaluation and management of SVA
Patients without documented arrhythmia
Diagnostic investigations
Additional evaluation
Patients with documented arrhythmia
Differential diagnosis for narrow QRS complex tachycardia (QRS duration <120 ms).
Differential diagnosis for wide QRS-complex tachycardia (QRS duration ≥120 ms)
Management
Specific arrhythmias
Sinus tachyarrhythmias
Physiological sinus tachycardia
Inappropriate sinus tachycardia
Sinus node re-entry tachycardia
Atrioventricular nodal reciprocating tachycardia (AVNRT)
Focal and nonparoxysmal junctional tachycardia
Focal junctional tachycardia
Nonparoxysmal junction tachycardia
AV re-entrant tachycardia
Focal atrial tachycardias
Atrial flutter
Special circumstances
Pregnancy
Future directions

Organization of committee and evidence review

In order to facilitate and optimize the management of patients with supraventricular arrhythmias, the American Heart Association (AHA), American College of Cardiology Foundation (ACCF), and the European Society of Cardiology (ESC) created a committee to establish guidelines for the management and treatment of patients with supraventricular arrhythmias (SVA), written in collaboration with the Heart Rhythm Society (HRS). The term supraventricular arrhythmias refers to rhythms emanating from the sinus node, from atrial tissue (focal atrial tachycardias, atrial flutter), from the atrioventricular (AV) node, as well as accessory pathway-mediated tachycardia. The document summarized recommendations for diagnostic procedures as well as indications for anti-arrhythmic drugs and/or nonpharmacological treatments. For the purpose of this handbook, a comprehensive review of relevant literature from 2003 to 2006 using the PubMed/MEDLINE and Cochrane Library databases was conducted, using English language sources and including studies in human subjects only. Anti-arrhythmic drug dosages are outlined in detail in the Atrial Fibrillation section, and are therefore not repeated.

General evaluation and management of SVA

Patients without documented arrhythmia

A clinical history of arrhythmia-related symptoms may give clues to the type of arrhythmia. Arrhythmia-related symptoms include palpitations, fatigue, lightheadedness, chest discomfort, dyspnea, presyncope or syncope. The clinician should distinguish whether the palpitations are regular or irregular:

• Irregular palpitations may be due to premature extra beats, atrial fibrillation (AF) or multifocal atrial tachycardia.

The AHA Guidelines and Scientific Statements Handbook
Edited by Valentin Fuster
ISBN: 978-1-405-18463-2

• Regular and recurrent palpitations with a sudden onset and termination are defined as paroxysmal supraventricular tachycardia (referred to as PSVT). Termination by vagal manoeuvres supports a re-entrant tachycardia involving AV nodal tissue (AV nodal reciprocating tachycardia (AVNRT) or atrioventricular reciprocating tachycardia (AVRT)).
• Sinus tachycardia is nonparoxysmal and accelerates and terminates gradually.
• Pauses or dropped beats followed by sensation of a strong heart beat support presence of premature beats.

Symptoms vary with the ventricular rate, underlying heart disease, duration of SVT, and individual patient perceptions. Important for clinical decision making is to describe the pattern in terms of the number of episodes, duration, frequency, mode of onset, and possible triggers.

Arrhythmias associated with bypass tracts may be life-threatening. A resting 12-lead electrocardiogram (ECG) should be recorded.

Diagnostic investigations

Electrocardiogram, to identify:
• Presence of abnormal rhythm.
• Preexcitation.
• Long QT interval.
• Evidence of underlying heart disease (myocardial infarction, hypertrophy, bundle branch block).

Additional evaluation

• 24-hour Holter monitoring: for frequent but transient symptoms of tachycardias (several episodes per week).
• Event loop recorder: for less frequent arrhythmias.
• Implantable loop recorders: are used for infrequent symptoms.
• Exercise testing: clear history of exercise-induced arrhythmia.
• Transesophageal atrial stimulation: to provoke paroxysmal tachyarrhythmias if other measures have failed to document an arrhythmia.
• Invasive electrophysiological study:
  – in patients with a clear history of regular and paroxysmal palpitations or disabling symptoms;
  – in cases with preexcitation on the 12-lead ECG and any symptoms of arrhythmia;
  – in patients with wide QRS tachycardia where diagnosis is uncertain. In combination with catheter ablation for treatment.

If the arrhythmia is paroxysmal in nature and there is no further clue for the arrhythmia mechanism, a beta-blocking agent may be prescribed empirically. Anti-arrhythmic agents with Class I or Class III properties should not be initiated without a documented arrhythmia, due to the risk of proarrhythmia.

Patients with documented arrhythmia

Classify the tachycardia as a narrow- or wide QRS complex tachycardia by measuring the QRS duration.

Differential diagnosis for narrow QRS complex tachycardia (QRS duration <120 ms)

These tachycardias are almost always supraventricular tachycardias (SVT). The relationship of the P-waves to the ventricular complex gives a clue to the diagnosis (Fig. 16.1). Responses of narrow QRS complex tachycardia to adenosine or carotid massage may aid in the differential diagnosis (Fig 16.2) [1].

Differential diagnosis for wide QRS-complex tachycardia (QRS duration ≥120 ms)

The differential diagnosis for wide QRS-complex tachycardia includes (Fig. 16.3):
• Ventricular tachycardia (VT).
• SVT with bundle-branch block or aberration.
• SVT with anterograde conduction over an accessory pathway.

If the QRS-complexes are identical to those during sinus rhythm consider either SVT with bundle-branch block, or antidromic AVRT. A history of myocardial infarction or structural heart disease supports VT. Ventricular fusion beats indicate a ventricular origin of the tachycardia. Ventriculoatrial dissociation with a ventricular rate faster than the atrial rate generally proves the diagnosis of VT, but is present in only 30% of all VTs. An analysis of QRS width and QRS configuration

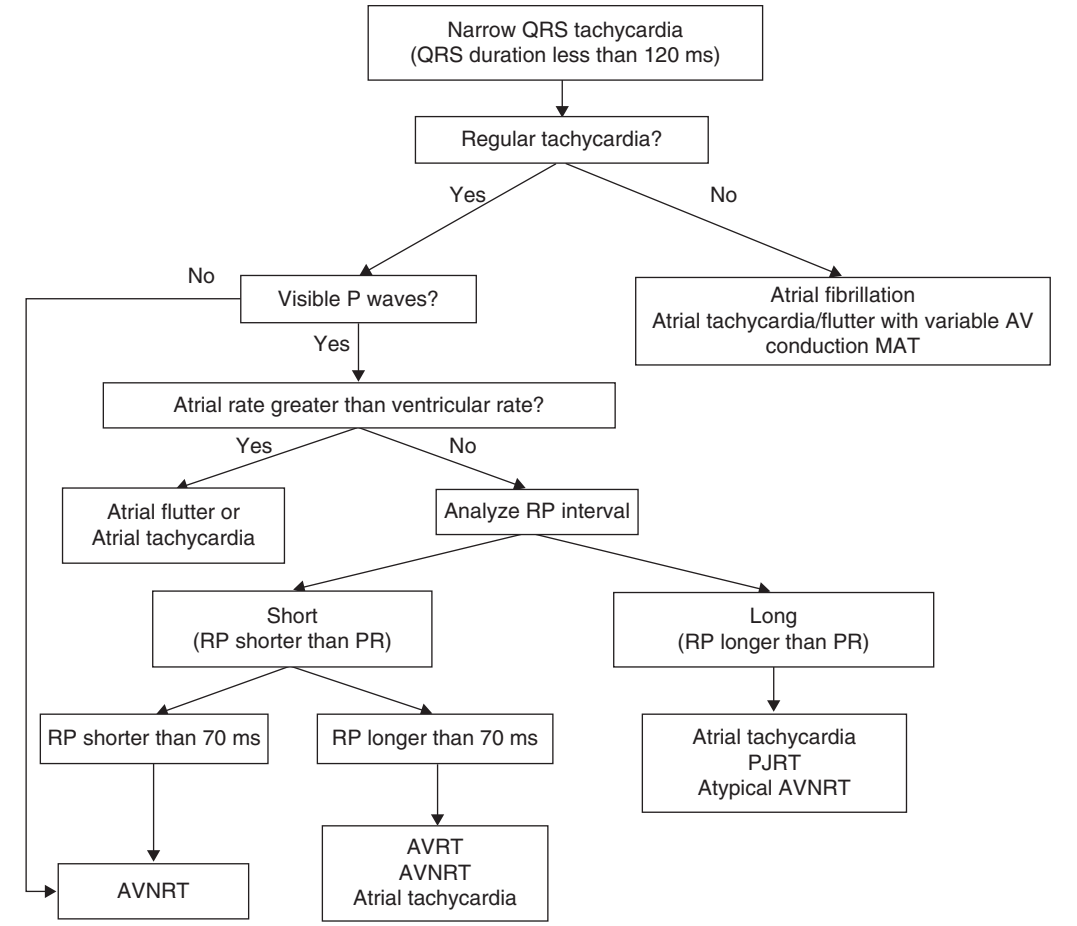

Fig. 16.1 Differential diagnosis for narrow QRS tachycardia. Patients with focal junctional tachycardia may mimic the pattern of slow–fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate. AV indicates atrioventricular; AVNRT, atrioventricular nodal reciprocating tachycardia; AVRT, atrioventricular reciprocating tachycardia; MAT, multifocal atrial tachycardia; ms, milliseconds, PJRT, permanent form of junctional reciprocating tachycardia; QRS, ventricular activation on ECG.

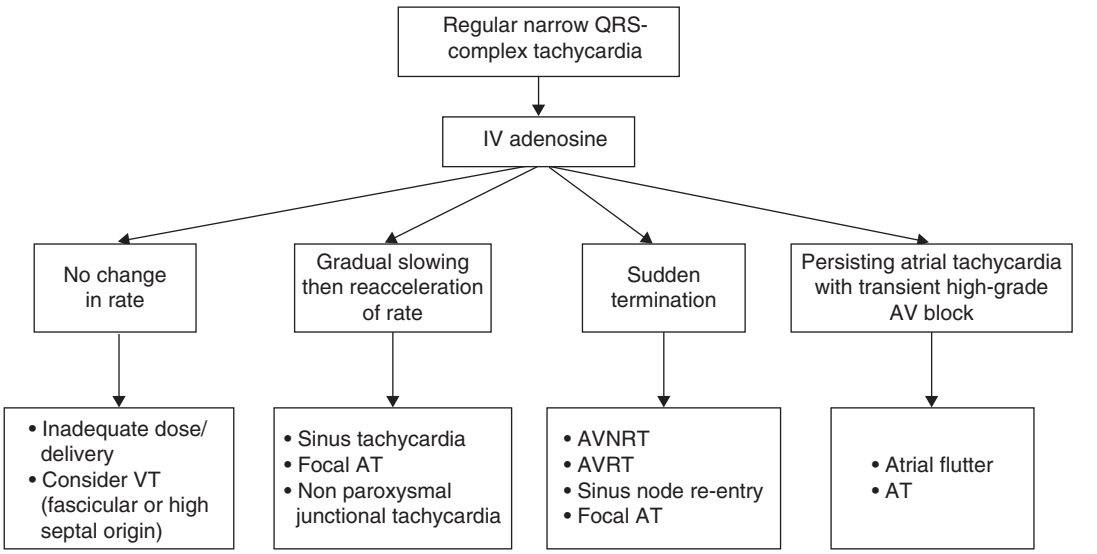

Fig. 16.2 Responses of narrow complex tachycardias to adenosine. AT indicates atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reciprocating tachycardia; AVRT, atrioventricular reciprocating tachycardia; IV, intravenous; QRS, ventricular activation on ECG; VT, ventricular tachycardia.

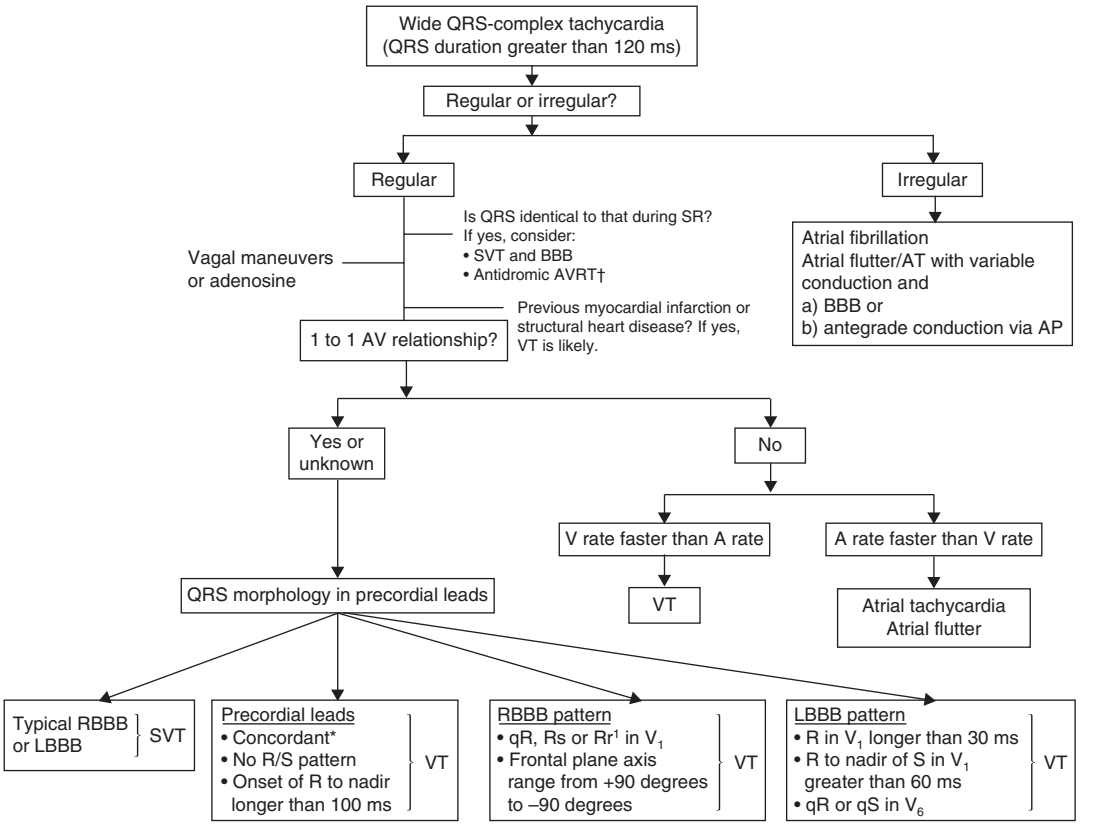

Fig. 16.3 Differential diagnosis for wide QRS-complex tachycardia (more than 120 ms). A QRS morphology analysis is of less value in the presence of QRS conduction delay during sinus rhythm. *Concordant indicates that all precordial leads show either positive or negative deflections. †In preexcited tachycardias, the QRS is generally wider (i.e., more preexcited) compared with sinus rhythm. A indicates atrial; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVRT, atrioventricular reciprocating tachycardia; BBB, bundle-branch block; LBBB, left bundle-branch block; ms, milliseconds; QRS, ventricular activation on ECG; RBBB, right bundle-branch block; SR, sinus rhythm; SVT, supraventricular tachycardias; V, ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

can be helpful in differentiating VT from SVT (Fig. 16.3).

Indications for referral to an arrhythmia specialist include:

- Patients with Wolf–Parkinson–White syndrome (presence of pre-excitation and arrhythmia).
- Patients with severe symptoms (syncope or dyspnea) during palpitations.
- Wide QRS-complex tachycardia of unknown origin.
- Narrow QRS-complex tachycardia with drug-resistance or intolerance, or patients desire to be free from drug therapy.

Management

If the diagnosis of SVT can not be proven, the patient should be treated as if VT was present. Medications for SVT (Verapamil or diltiazem) may precipitate hemodynamic collapse for a patient with VT. Adenosine should be used with caution when the diagnosis is unclear, because it may produce VF in patients with coronary artery disease. Adenosine may also precipitate AF with a rapid ventricular rate in patients with preexcitation. Immediate DC cardioversion is the treatment for hemodynamically unstable tachycardias. Recommendations for acute

Table 16.1 Recommendations for acute management of hemodynamically stable and regular tachycardia

ECG	Recommendation*	Classification	Level of evidence
Narrow QRS complex tachycardia (SVT)	Vagal maneuvers	I	B
	Adenosine	I	A
	Verapamil/diltiazem	I	A
	Beta-blockers	IIb	C
	Amiodarone	IIb	C
	Digoxin	IIb	C
Wide QRS complex tachycardia			
• SVT + BBB	See above		
• Preexcited SVT/AF	Flecainide‡	I	B
	Ibutilide‡	I	B
	Procainamide‡	I	B
	DC cardioversion	I	C
• Wide QRS complex tachycardia of unknown origin	Procainamide‡	I	B
	Sotalol‡	I	B
	Amiodarone	I	B
	DC cardioversion	I	B
	Lidocaine	IIb	B
	Adenosine§	IIb	C
	Beta-blockers¶	III	C
	Verapamil**	III	B
• Wide QRS complex tachycardia of unknown origin in patients with poor LV function	Amiodarone	I	B
	DC cardioversion,	I	B
	Lidocaine	I	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration.

* All listed drugs are administered intravenously.

‡ Should not be taken by patients with reduced LV function.

§ Adenosine should be used with caution in patients with severe coronary artery disease because vasodilation of normal coronary vessels may produce ischemia in vulnerable territory. It should be used only with full resuscitative equipment available.

¶ Beta blockers may be used as first-line therapy for those with catecholamine-sensitive tachycardias, such as right ventricular outflow tachycardia.

** Verapamil may be used as first-line therapy for those with LV fascicular VT.

AF indicates atrial fibrillation; BBB, bundle-branch block; DC, direct current; ECG, electrocardiogram; LV, left ventricular; QRS, ventricular activation on ECG; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

management of hemodynamically stable and regular tachycardia are shown in Table 16.1 [2–4].

Specific arrhythmias

Sinus tachyarrhythmias

Physiological sinus tachycardia

Sinus tachycardia is defined as an increase in sinus rate to more than 100 bpm in response to physical, emotional, pathological, or pharmacological stress. It is nonparoxysmal, thus differentiating it from re-entry. The P waves are positive in leads I–II and aVF, and negative in AVR. The frontal plane axis is between 0 and +90, and can be negative in leads V1 and V2 but positive in leads V3 to V6. Several pathological conditions may cause sinus tachycardia including pyrexia, hypovolemia, anemia, or certain drugs (salbutamol, aminophylline, atropine,

catecholamines) or stimulants (e.g., caffeine, alcohol, nicotine). It may also reflect severe underlying pathologies.

The management of sinus tachycardias primarily involves identifying the cause and either eliminating or treating it.

Inappropriate sinus tachycardia

Inappropriate sinus tachycardia is a persistent and exaggerated increase in resting heart rate unrelated to the level of physical, emotional, pathological, or pharmacological stress.

Diagnostic criteria

- Persistent sinus tachycardia (heart rate above 100 bpm) during daytime with excessive rate increase in response to activity and nocturnal normalization of rate (confirmed by 24-hour Holter recording).
- The tachycardia and symptoms are not paroxysmal.
- P-wave morphology and intracardiac activation is identical to sinus rhythm [5].
- A secondary systemic cause is excluded.

Treatment

The treatment is predominantly symptom-driven (Table 16.2). The long-term heart rate control after sinus node modification by catheter ablation has been reported to be around 66% [6]. A recent smaller study using a noncontact mapping system demonstrated effective heart rate control in six of seven patients [7]. Complications related to catheter ablation include superior vena cava (SVC) occlusion, phrenic nerve paralysis, and permanent pacemaker requirement. The diagnosis of postural orthostatic tachycardia syndrome (POTS) must be excluded before considering ablation. Recommendations are outlined in Table 16.2.

Sinus node re-entry tachycardia

Sinus node re-entry tachycardia arises from re-entrant circuits within or close to the sinus node leading to paroxysmal or nonsustained bursts of tachycardia that are similar to those in sinus rhythm.

Clinical criteria include:

- The tachycardia and associated symptoms are paroxysmal and the P-wave morphology is identical to sinus rhythm.
- The arrhythmia may be terminated by vagal maneuvers or adenosine.
- Intracardiac atrial activation sequence is similar to that of sinus rhythm [5].
- Premature atrial stimuli can induce and/or terminate the arrhythmia.
- Induction of the arrhythmia is not dependent on a critical AV-nodal conduction time.

Treatment

Patients with well-tolerated tachyarrhythmias that are controlled by vagal maneuvers and/or drug therapy should not be considered for catheter ablation. Catheter ablation, albeit generally successful, should be reserved for medically refractory cases [8].

Atrioventricular nodal reciprocating tachycardia (AVNRT)

AVNRT, the most common form of PSVT, is a re-entry tachycardia involving the AV node and perinodal atrial tissue. Most commonly the fast pathway is located near the superior portion of the AV node and the slow pathway along the septal margin of the tricuspid annulus at the level of the coronary sinus. During typical AVNRT (85–90%) the anterograde conduction occurs over the slow pathway and the

Table 16.2 Recommendations for treatment of inappropriate sinus tachycardia

Treatment	Agents/procedure	Classification	Level of evidence
Medical	Beta-blockers	I	C
	verapamil; diltiazem	IIa	C
Catheter ablation	Catheter ablation – sinus node modification/elimination	IIb	C

retrograde conduction occurs over the fast pathway (slow-fast AV node re-entry). Less commonly (5–10%) the tachycardia circuit is reversed resulting in a long R-P tachycardia (i.e., fast-slow AVNRT or atypical AVNRT), with negative P waves in lead III and aVF inscribed prior to the QRS. In slow–slow AVNRT, the retrograde atrial activation first occurs over the slow pathway region once the RP interval is greater than 70 ms.

Treatment

The treatment of AVNRT is predominantly symptom-driven (Table 16.3). The choice between drugs (AV-nodal blocking agents) vs. catheter ablation is often governed by patient preference and clinical judgment. The drug efficacy is approximately 30–50% [9–12].

Single-dose therapy ("pill-in-the-pocket") may be considered for patients with infrequent, well-tolerated

Table 16.3 Recommendations for long-term treatment of patients with recurrent AVNRT

Clinical presentation	Recommendation	Class	Level of evidence
Poorly tolerated AVNRT with hemodynamic intolerance	Catheter ablation	I	B
	Verapamil, diltiazem, beta-blocker, sotalol, amiodarone	IIa	C
	Flecainide*, propafenone*	IIa	C
Recurrent symptomatic AVNRT	Catheter ablation	I	B
	Verapamil	I	B
	Diltiazem, beta-blocker	I	C
	Digoxin†	IIb	C
Recurrent AVNRT unresponsive to beta-blockade or calcium channel blocker and patient not desiring RF ablation	Flecainide,* propafenone,* sotalol	IIa	B
	Amiodarone	IIb	C
AVNRT with infrequent or single episode in patients who desire complete control of arrhythmia	Catheter ablation	I	B
Documented PSVT with only dual AV nodal pathways or single echo beats demonstrated during electrophysiologic study and no other identified cause of arrhythmia	Verapamil, diltiazem, beta-blockers, flecanide†, propafenone*	I	C
	Catheter ablation‡	I	B
Infrequent, well-tolerated AVNRT	No therapy	I	C
	Vagal maneuvers	I	B
	"Pill-in-the-pocket"	I	B
	Verapamil, diltiazem, beta-blockers	I	B
	Catheter ablation	I	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration.

*Relatively contraindicated in patients with coronary artery disease, left ventricular dysfunction, or other significant heart disease.

†Digoxin is often ineffective because its pharmacologic effects can be overridden by enhanced sympathetic tone.

‡Decision depends on symptoms.

AV, atrioventricular; AVNRT, atrioventricular nodal reciprocating tachycardia; PSVT, paroxysmal supraventricular tachycardia; RF, radiofrequency.

but long-lasting episodes of AVNRT when vagal maneuvers alone are ineffective for the termination of tachycardia episodes. Candidates should have normal left ventricular function, no bradycardia and no preexcitation. Oral single-dose of diltiazem (120 mg) plus propranolol (80 mg) was more effective in terminating PSVT than both placebo and flecainide [13].

Radiofrequency (RF) catheter ablation is successful in 96% [14–16]. Ablation of the slow pathway, which is the preferable approach, has markedly reduced the risk of AV-block to less than 1%. In one long-term follow-up (10 years) study after RF ablation no AVNRT recurrences were observed, but 24% suffered from new arrhythmias or late AV block [17].

Slow pathway cryoablation has been associated with higher recurrence rates than radiofrequency ablation (7–20% vs. 5.6%) in some studies [18,19]. AV-block is not guaranteed by negative cryomapping, stressing the need for careful surveillance [18]. Newer concepts relative to pathogenesis of AVNRT relate to involvement of the right and left inferior nodal extensions. These concepts explain the need for ablation of AVNRT (in rare patients) from the coronary sinus or mitral annulus [20].

Focal and nonparoxysmal junctional tachycardia

Focal junctional tachycardia

Other terms for this tachycardia are automatic or junctional ectopic tachycardia. The arrhythmia origin is the AV node or His bundle. The abnormally rapid discharges from the junctional region results in varied ECG manifestations because it does not require participation of either the atrium or the ventricle for its propagation. The heart rate ranges between 110 and 250 bpm, with narrow or typical bundle branch block conduction pattern. Atrioventricular dissociation is often present. The arrhythmia is rare and seen in young adults. It is usually exercise or stress-related, and may occur in patients with structurally normal hearts or in patients with congenital abnormalities. It may, if untreated, produce congestive heart failure, especially if it is incessant.

Drug therapy is only variably successful [21]. Catheter ablation is associated with risk of AV-block [22,23] (Table 16.4).

Nonparoxysmal junction tachycardia

This is a benign arrhythmia characterized by narrow complex tachycardia with rates of 70–120 bpm. The arrhythmia may be a marker for serious underlying conditions (digitalis toxicity, postcardiac surgery, hypokalemia or myocardial ischemia) and may be observed in conjunction with chronic obstructive lung disease with hypoxia, and inflammatory myocarditis. It shows a typical "warm-up" and "cool-down" pattern and cannot be terminated by pacing maneuvers. Unlike the more rapid form of focal

Table 16.4 Recommendations for the treatment of focal and nonparoxysmal junctional tachycardia syndromes

Tachycardia	Recommendation	Classification	Level of evidence
Focal junctional tachycardia	Beta-blocker	IIa	C
	Flecainide	IIa	C
	Propafenone*	IIa	C
	Sotalol*	IIa	C
	Amiodarone*	IIa	C
	Catheter ablation	IIa	C
Nonparoxysmal junctional tachycardia	Reverse digitalis toxicity	I	C
	Correct hypokalemia	I	C
	Treat myocardial ischemia	I	C
	Beta-blockers, calcium channel blockers	IIa	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration.

*Data available for pediatric patients only.

junctional tachycardia, there is commonly one-to-one AV association.

Treatment should be directed at the underlying condition (Table 16.4).

AV re-entrant tachycardia

Accessory pathways are muscle fibers that connect the atrium with the ventricle. Pathways that are capable of antegrade conduction to the ventricle are termed "manifest" and are present in 0.15–0.25% of the general population. Other pathways conduct retrogradely only and are known as "concealed".

Approximately 95% of the arrhythmias in patients with the Wolff–Parkinson–White (WPW) syndrome are manifest as "orthodromic" tachycardias (antegrade conduction over the normal AV node–His axis and retrograde over the accessory pathway). About 5% involve "antidromic" tachycardia with antegrade conduction over the pathway and retrograde over the node. A less common form of tachycardia is labeled PJRT and involves retrograde conduction over a decremental pathway in the posteroseptal region.

The most feared rhythm occurring in patients with WPW is atrial fibrillation, occurring over a pathway with short refractory period capable of rapid conduction to the ventricle. This arrhythmia is potentially life-threatening. Risk factors include shortest preexcited RR interval during atrial fibrillation of <250 ms, multiple pathways, history of rapid tachycardia and Ebstein's anomaly.

Acute treatment

Emergency therapy for those with orthodromic tachycardia involves use of carotid massage and/or adenosine. Agents that block atrioventricular (AV) nodal conduction (i.e. IV Ca^{++} channel blockers or beta-blockers may be effective). Treatment for those with rapid preexcited atrial fibrillation include IV procainamide or ibutilide, if the patient is stable and emergency direct-current shock if the patient has hemodynamic instability.

Long-term therapy

Long-term drug therapy has been increasingly replaced by catheter ablation of the pathways. The most effective drug regimen is use of a combination of a Class 1 C agent (propafenone or flecainide) and a beta-blocker agent. Catheter ablation is successful in approximately 95% of cases and is associated with significant adverse effects in 1.8–4% including a 0.08–0.13% risk of death (see Table 16.5).

Since publication of the guidelines a prospective study designed to assess the efficacy of an experimental Class II agent (azimilide) for patients with various supraventricular arrhythmias has been published [24]. The study contained 56 patients with PSVT and they found no significant difference in the time to recurrence of symptoms between treated patients (18 days) vs. the placebo group (35 days). The authors concluded that the 125 mg daily dose of azimilide did not confer a beneficial effect compared with placebo treatment.

Recent advances include refinement of ablative techniques to allow for ablation of anteroseptal accessory pathways that could not be ablated via a right or left sided approach. The pathway could be ablated from the noncoronary cusp of the aortic valve [25]. Other newer ablative techniques involve use of navigational systems to allow for more precise mapping [26], use of cryoablation for pathways close to the His bundle [27], or the introduction of epicardial approaches for pathway ablation [28].

Treatment of asymptomatic subjects

The treatment of asymptomatic patients with accessory pathways remains controversial. Given the very low incidence of sudden death as the primary arrhythmia event and the very low positive predictive value of invasive studies, it is felt that routine ablation of these pathways are not warranted. The decision to ablate the pathway(s) in those with high-risk occupations (i.e. pilots) should be made on individual considerations.

Focal atrial tachycardias

Focal atrial tachycardias (FAT) are identified in the laboratory by radial spread of activation from a discrete focus. These tachycardias do not occur randomly throughout the atria, but have several sites of predilection. In the right atrium favored sites include the crista terminalis, peri-annular region, septum and the os of the coronary sinus. In the left atrium sites of predilection include the pulmonary veins, mitral annulus and appendage. The mechanism of atrial tachycardia may be due to triggered rhythms, abnormal automaticity or micro re-entry. Even in the laboratory setting it is often difficult to

Table 16.5 Recommendations for long-term therapy of accessory pathway-mediated arrhythmias

Arrhythmia	Recommendation	Classification	Level of evidence
WPW syndrome preexcitation and symptomatic arrhythmias, well tolerated	Catheter ablation	I	B
	Flecainide, propafenone	IIa	C
	Sotalol, amiodarone, beta-blockers	Ia	C
	Verapamil, diltiazem, digoxin	II	C
WPW syndrome (with AF and rapid-conduction or poorly tolerated AVRT)	Catheter ablation	I	B
AVRT, poorly tolerated (no preexcitation)	Catheter ablation	I	B
	Flecainide, propafenone	IIa	C
	Sotalol, amiodarone	IIa	C
	Beta-blockers	IIb	C
	Verapamil, diltiazem, digoxin	II	C
Single or infrequent AVRT episode(s) (no preexcitation)	None	I	C
	Vagal maneuvers	I	B
	Pill-in-the-pocket – verapamil, diltiazem, beta-blockers	I	B
	Catheter ablation	Ia	B
	Sotalol, amiodarone	IIb	B
	Flecainide, propafenone	IIb	C
	Digoxin	II	C
Preexcitation, asymptomatic	None	I	C
	Catheter ablation	Ia	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

AF indicates atrial fibrillation; AVRT, atrioventricular reciprocating tachycardia; WPW, Wolff–Parkinson–White.

distinguish micro re-entry from abnormal automaticity. Incessant atrial tachycardia is usually seen in children or young adults and may produce a tachycardic myopathy.

Diagnoses

The diagnoses should be suspected when the patient presents with a long RP tachycardia where the P wave is different from sinus and is not compatible with retrograde activation from the AV node. In addition, if adenosine results in AV block with persistence of tachycardia, then the diagnoses is almost always atrial tachycardia.

Treatment

Acute therapy of FAT includes initial trials of adenosine (effective in 20–30% of cases) or other AV nodal blockers (beta-blockers or Ca^{++} channel blockers). The latter drugs seldom terminate the tachycardia, but may be used to achieve rate control by AV nodal blockade. Direct-current

cardioversion is often ineffective, but may result in termination of micro re-entrant or triggered atrial rhythms.

Long-term management of FAT involves initial trials of AV nodal blocking agents; failing this approach one can try Class iC agents (flecainide/propafenone) or sotalol or amiodarone. Catheter ablation may be used as primary therapy for these patients (Table 16.6). Catheter ablation is associated with 80–90% success rate for right atrial foci and 70–80% success rate for left atrial foci. The incidence of complications is low (1%) and includes AV block for septal foci and complication related to the transseptal procedure and left atrial ablation (see Table 16.6).

Newer studies related to patients with FAT have involved better application of atrial site localization by means of surface ECG criteria [29]. In addition an exciting new technique involving detection of the atrial focus by means of multi-electrode surface

Table 16.6 Recommendation for treatment of focal atrial tachycardia

Clinical situation	Recommendation	Classification	Level of evidence
Acute treatment†			
A. Conversion			
Hemodynamically unstable patient	DC cardioversion	I	B
Hemodynamically stable patient	Adenosine	IIa	C
	Beta blockers	IIa	C
	Verapamil, diltiazem	IIa	C
	Procainamide	IIa	C
	Flecainide/propafenone	IIa	C
	Amiodarone, sotalol	IIa	C
B. Rate regulation* (in absence of digitalis therapy)	Beta blockers	I	C
	Verapamil, diltiazem	I	C
	Digoxin	IIb	C
Prophylactic therapy			
Recurrent symptomatic AT	Catheter ablation	I	B
	Beta blockers, calcium-channel blockers	I	C
	Disopyramide‡	IIa	C
	Flecainide/propafenone‡	IIa	C
	Sotalol, amiodarone	IIa	C
Asymtomatic and symtomatic incessant AIs	Catheter ablation	I	B
Nonsustained and asymptomatic	No therapy	I	C
	Catheter ablation	III	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

*Excluded are patients with MAT in whom beta-blockers and sotalol are often contraindicated due to pulmonary disease.

†All listed drugs for acute treatment are administered intravenously.

‡Flecainide, propafenone, and disopyramide should not be used unless they are combined with an AV-nodal–blocking agent.

AF indicates strial tachycardia; DC, direct current; MAT, multifocal atrial tachycardia.

mapping (ECGI) and solving the inverse relationship appear promising [30]. Other studies have focused on use of adenosine to determine the tachycardia mechanism. Adenosine appears to terminate triggered rhythms, depress automatic rhythms and appears to have no effect on those with micro reentry [31]. In addition, efforts to improve techniques for ablation of anteroseptal foci include introduction of a technique to ablate anteroseptal foci from the noncoronary cusp of the aortic valve [32].

Atrial flutter

Atrial flutter is rapid macro re-entrant atrial tachycardia with atrial rates between 250 and 350 beats/minute. Atrial flutter usually involves the muscles around the tricuspid annulus. The most common form is counter clockwise activation (LAO projection) around the annulus with the crista terminalis and subeustachian ridge acting as the posterior barrier. A less common form involves clockwise activation around the annulus. Both of these forms involve the cavotricuspid isthmus and this area serves as the target for ablation.

Non-CTI dependent flutter is most often seen after corrective surgery for congenital cardiac disease or following left atrial ablation for atrial fibrillation. These circuits involve activation around scars and/or pulmonary venous sites. In addition, atypical flutter may involve the muscles around the mitral annulus or over the left atrial septum.

Treatment

Acute therapy is dictated by the patient's hemodynamic status. Emergency intervention includes use of atrial overdrive pacing or low energy (20–50 watts) direct current cardioversion. In more urgent situations use of AV nodal blocking agents for rate stabilization is indicated. This is especially important for those in whom Class 1 C drugs are contemplated, since IC drugs may slow the atrial rate and result in paradoxical increase in the ventricular response unless nodal conduction is attenuated. The most effective drug for acute conversion of atrial flutter is intravenous ibutilide (38–76% efficacy rate). Acute therapy is summarized in Table 16.7.

Chronic therapy

Chronic drug therapy is often ineffective. Class III agents especially dofetilide appear to be more effective than Class 1 C drugs, since the latter appear to stabilize the flutter circuit by decreasing atrial conduction velocity.

Catheter ablation has proved to be 95% effective for those with CTI dependent flutter and has become the cornerstone of treatment for this arrhythmia. Ablation for nonisthmus dependent flutter is less successful since multiple circuits involving multiple scars are often found. The success rate will be governed by circuit numbers and complexity. See Table 16.8.

Since publication of the guidelines, a number of studies comparing drug therapy or drug vs. ablative therapy have been reported. In two multicenter double-blind randomized trials [33], the efficacy of dronedarone (amiodarone derivative) was evaluated for patients treated with 400 mg twice per day vs. 409 patients treated with placebo. The patients had either atrial fibrillation and/or atrial flutter. In both trials there was a significant increase in time to first recurrence of either atrial fibrillation or flutter. This study provides evidence for a new drug approach for management of patients with atrial flutter.

A recent prospective randomized study by Kafkas *et al.* [34] compared conversion rates of recent onset atrial fibrillation or atrial flutter in patients treated with IV amiodarone vs. IV ibutilide. For the patients with atrial flutter, ibutilide was significantly superior to amiodarone (87% vs. 29%) ($P < 0.003$) in conversion to sinus rhythm. This study strengthens guideline recommendations for acute treatment of atrial flutter.

A randomized prospective study [35] compared amiodarone treatment vs. ablation after only the initial episode of symptomatic cavotricuspid isthmus flutter. The study included 104 patients who were randomized to the two treatment arms. Better long-term success rates (in terms of maintenance of sinus rhythm) were achieved for the group treated with ablation.

A number of studies have focused on long-term follow-up of patients treated with radiofrequency ablation of the cavotricuspid isthmus for typical

Table 16.7 Recommendation for acute management of atrial flutter

Clinical status proposed therapy	Recommendation*	Classification	Level of evidence
Poorly tolerated			
• Conversion	DC cardioversion	I	C
• Rate control	Beta-blockers	IIa	C
	Verapamil or diltiazem	IIa	C
	Digitalis†	Ib	C
	Amiodarone	Ib	C
Stable flutter			
• Conversion	Atrial or transesophageal pacing	I	A
	DC cardioversion	I	C
	Butilide‡	IIa	A
	Flecainide§	Ib	A
	Propafenone§	Ib	A
	Sotalol	Ib	C
	Procainamide§	Ib	A
	Amiodarone	Ib	C
• Rate control	Diltiazem or verapamil	I	A
	Beta-blockers	I	C
	Digitalis†	Ib	C
	Amiodarone	Ib	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

Cardioversion should be considered only if the patient is anticoagulanted (NR equals 2 to 3), the arrhythmia is less than 48 hours in duration, or the TEE shows no atrial clots.

*All drugs are administered intravenously.

†Digitalis may be especially useful for rate control in patients with heart failure.

‡Ibutilide should not be taken by patients with reduced LV function.

§Flecainide, propafenone, and procainamide should not be used unless they are combined with an AV-nodal–blocking agent.

AV indicates atrioventricular; DC, direct current; INR, international normalized ratio; LV left ventricular; TEE, transesophageal echocardiography.

atrial flutter. In a retrospective study [36] of patients who underwent ablation, 80 patients had no prior history of atrial fibrillation but 40 (50%) developed atrial fibrillation after a mean follow-up of 29.6 months. The incidence of fibrillation was progressive with 40% occurring after 2 years. Moreover, the authors found no difference in age, left atrial size or presence of structural heart disease between those that developed atrial fibrillation or who did not.

Similarly, Meissner *et al.* [37] found a 59.1% recurrence rate of atrial fibrillation after a mean follow-up of 3 years. The authors concluded that in spite of the high rate of progression to atrial fibrillation, there was a significant symptomatic benefit and daily work activities and need for hospitalization was reduced.

Although the longer term follow-up data suggest development of a very high incidence of atrial fibrillation, ablation is still indicated as primary therapy for flutter, because of better arrhythmia control compared with drug therapy and because atrial flutter may be associated with higher ventricular rates and more symptoms than attacks of atrial fibrillation.

Table 16.8 Recommendation for long-term management of atrial flutter

Clinical status/proposed therapy	Recommendation	Classification	Level of evidence
First episode and well-tolerated atrial flutter	Cardoversion alone	I	B
	Catheter ablation*	IIa	B
Recurrent and well-tolerated atrial flutter	Catheter ablation*	I	B
	Dofetilide	IIa	C
	Amiodarone, sotalol, flecainide,†‡ quinidine,†‡ properafenone,†‡ procainamide,†‡ disopyramide†‡	IIb	C
Poorly tolerated atrial flutter	Catheter ablation*	I	B
Atrial flutter appearing after use of class Ic agents or amiodarone for treatment of AF	Catheter ablation*	I	B
	Stop current drug and use another	IIa	C
Symptomatic non-CTI-dependent flutter after failed antiarrhythmic drug therapy	Catheter ablation*	IIa	B

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

* Catheter ablation of the AV junction and insertion of a pacemaker should be considered if catheter ablation cure is not possible and the patient fails drug therapy.

† These drugs should not be taken by patients with significant structural cardiac disease. Use of anticoagulants is identical to that described for patients with AF(http://www.acc.org/clinical/guidelines/atrial_fib/af_index.htm).***

‡ Flecainide, propafenone, procainamide, quinidine, and disopyramide should not be used unless they are combined with an AV-nodal-blocking agent.

AF indicates atrial flixillation; AV, atrioventricular; CTI, cavotricuspid isthmus.

Table 16.9 Recommendations for treatment strategies for SVT during pregnancy

Treatment strategy	Recommendation	Classification	Level of evidence
Acute conversation of PSVT	Vagel maneuver	I	C
	Adenosine	I	C
	DC cardioversion	I	C
	Metoprolol, propranolol	IIa	C
	Verapamil	Ib	C
Prophylactic therapy	Digoxin	I	C
	Metoprolol*	I	B
	Propranolol*	IIa	B
	Sotalol,* flecainide†	IIa	C
	Quinidine,propafenone,† verapamil	Ib	C
	Procainamide	Ib	B
	Catheter ablation	Ib	C
	Atenolol‡	II	B
	Amiodarone	II	C

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

* Beta-blocking agents should not be taken in the first trimaster, if possible.

† Consider AV-nodal–blocking agents in conjunction with flecainide and propatenone for certain tachycardias (see Section V).

‡ Atenolol is categorized in class C (drug classification for use during pregnancy) by legal authorities in some European countries.

AV indicates atrioventricular; DC, direct current; PSVT, paroxysmal supraventricular tachycardia.

Special circumstances

Pregnancy

There is concern about adverse hemodynamic effects of cardiac arrhythmias during pregnancy. In addition, there is concern about the tetragenic effects of cardiovascular agents (especially within the first 2 months). It is important to consider ablation procedures for care of arrhythmias prior to pregnancy. In terms of acute management of SVA, use of vagal maneuvers adenosine or D/C shock for acute cardioversion of SVA is safe for both mother and fetus. Other drugs used for acute treatment are listed in Table 16.9.

Chronic therapy should be used only if symptoms are intolerable or if the tachycardia results in hemodynamic compromise. In resistant cases, catheter ablation may be used as a last resort, always mindful to expose mother and fetus to minimal radiologic exposure.

Since publication of the guidelines, the safety in use of ibutilide has been reported [38]. In addition, several studies have shown the efficacy of ablative procedures for drug resistant cases of SVT [39,40].

Future directions

There are a number of projected exciting future developments related to SVT.

In the future we look forward to modifications in the computerized surface ECG analyses of rhythm disturbances allowing for ready incorporation of the existing criteria as described in the text. For example, electronic caliper measurements of specific ECG forms during tachycardia will facilitate arrhythmia diagnoses. In addition, newer diagnostic pacing techniques allow for more efficient and accurate diagnoses of the types of SVT encountered in the catheter laboratory. As our knowledge in this area grows we anticipate a broader range of diagnostic maneuvers to help pinpoint the diagnoses of the more complex arrhythmias particularly the left atrial scar-related flutters.

Newer drugs are currently being actively tested, particularly for patients with atrial fibrillation and flutter. These drugs include dronedarone, a homologue of amiodarone, which has been found to be effective but without major toxicities found to be associated with the parent drug.

Hopefully, a derivative of dronedarone will prove effective and safe for those patients with congestive heart failure. In addition, there is great interest in the development of drugs which are atriospecific. These agents exert their primary actions on atrial rather than ventricular tissue and hopefully avoid the development of torsades. One such agent is currently under review (Vernakalant) and appears to be effective and safe for acute conversion of atrial fibrillation and flutter. This drug may serve as the forerunner for a whole new approach for drug management of SVT.

There have been enormous strides in refinement of catheter ablative techniques which hold much promise for the future. These techniques include use of robotics or stereotaxis for precise catheter manipulation. Use of these techniques allow for the clinician to better manage complex SVT problems, as our found in patients with postatrial fibrillation ablation scars, as well as for complex surgical congenital corrections complicated by SVT. In addition, ablation of these complex arrhythmias are also facilitated by integration of CT anatomical details with intracardiac mapping tools.

These advances will allow for more precise definition and treatment of complex supraventricular arrhythmias. In addition to better mapping tools, a number of centers are experimenting with newer energy forms including laser, high energy ultrasound and microwave. The successful marriage of industry and interventional cardiac electrophysiology portends the development of tools that will allow for better treatment for these patients.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: Sleep Apnea and Cardiovascular Disease, http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.189420.

17 Ventricular Arrhythmias and Sudden Cardiac Death

A. John Camm and Douglas P. Zipes

Organization of committee and evidence review
Recommendations by various organizations for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death
Noninvasive evaluation
Resting electrocardiogram
Exercise testing
Ambulatory electrocardiography
Electrocardiographic techniques and measurements
Left ventricular function and imaging
Electrophysiological testing
Electrophysiological testing in patients with syncope
Ablation
Acute management of specific arrhythmias
Management of cardiac arrest
Ventricular tachycardia associated with low troponin myocardial infarction
Sustained monomorphic ventricular tachycardia
Repetitive monomorphic ventricular tachycardia
Polymorphic VT
Torsades de pointes
Incessant ventricular tachycardia
Ventricular arrhythmia and sudden cardiac death related to specific pathology
Left ventricular dysfunction due to prior myocardial infarction
Valvular heart disease
Congenital heart disease
Myocarditis, rheumatic disease, and endocarditis
Infiltrative cardiomyopathies
Endocrine disorders and diabetes
End-stage renal failure
Obesity, dieting, and anorexia
Pulmonary arterial hypertension
Transient arrhythmias of reversible cause
Ventricular arrhythmias associated with cardiomyopathies
Dilated cardiomyopathy (nonischemic)
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Neuromuscular disorders
Heart failure
Genetic arrhythmia syndromes
Long QT syndrome
Brugada syndrome
Catecholaminergic polymorphic ventricular tachycardia
Arrhythmias in structurally normal hearts
Idiopathic ventricular tachycardia
Electrolyte disturbances
Alcohol
Smoking
Lipids
Ventricular arrhythmias and sudden cardiac death related to specific populations
Athletes
Gender and pregnancy
Elderly patients
Pediatric patients
Patients with implantable cardioverter–defibrillators
Digitalis toxicity
Drug-induced long QT syndrome
Sodium channel blocker-related toxicity
Other drug-induced toxicity
Ongoing trials and future directions

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Organization of committee and evidence review

This guideline was produced under the auspices of the American Heart Association, the American College of Cardiology and the European Society of Cardiology. The Heart Rhythm Society and the European Heart Rhythm Association also provided writing committee members. The Guideline was

Table 17.1 Pathologies, arrhythmias, investigations, therapies and specific groups considered in these guidelines

Pathologies	Clinical presentations	Investigations	Therapies	Specific Groups
Acute coronary syndrome	Acute specific arrhythmias	ECG	Drug therapy	Gender
Heart failure	Ventricular tachycardia	Exercise testing	ICD and AED	Pediatric
Congenital heart disease	Ventricular fibrillation	Echocardiography	Ablation	Elderly
Cardiomyopathy	Torsades de pointes	Imaging	Surgery	Athletes
Endocrine disorders	Drug-induced arrhythmias	Electrophysiological testing	Resuscit-ation	Genetic arrhythmias
Myocarditis	Structurally normal hearts			Renal failure

chaired by A. John Camm, MD, and Douglas P. Zipes, MD. It was reviewed by official reviewers, two nominated by the ACC, two by the AHA, two by the ESC, one from the ACC/AHA Task Force on Practice Guidelines, reviewers from the EHRA and HRS, and 18 content reviewers, including members from ACCF Clinical Electrophysiology Committee, AHA Council on Clinical Cardiology, Electrocardiography, and Arrhythmias, and AHA Advanced Cardiac Life Support Subcommittee.

The guideline process included a comprehensive search of the scientific and medical literature on ventricular arrhythmias and sudden cardiac death (SCD) (limited to publications on humans and in English from 1990 to 2006). Specific targeted searches were performed on ventricular arrhythmias and SCD and a variety of subtopics (Table 17.1).

The final recommendations for each indication were derived from both clinical evidence and expert opinion and were classified in the agreed ACC/AHA/ESC format.

Recommendations by various organizations for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

There have been several guidelines dealing with the management of sudden death and ventricular arrhythmias, particularly using implantable devices [1–7]. Others have followed the publication of these guidelines [8].

The guideline writers faced a particular problem; European Heart Failure Guidelines had made management recommendations based on measurements below a range of ejection fractions (EFs). Others had used specific single EF cut-points. Thus recommendations for prophylactic ICD implantation based on EFs had been inconsistent (Table 17.2) because clinical investigators had chosen different EFs for enrollment in trials of therapy, average values of the EF in such trials have been substantially lower than the cut-off value for enrollment, and subgroup analyses of clinical trial populations based on EF have not been consistent in their implications. Substantial differences between guidelines have resulted. However, no trial has randomized patients with an intermediate range of EFs. For instance, there is no trial that has specifically studied patients with an LVEF between 31% and 35% and hardly any trial has specifically reported data relating to patients with EFs in this range, yet recommendations have been set for such patients on the basis of data derived from trials that studied groups with EFs less than or equal to 30%, others that enrolled patients with an EF less than or equal to 35%, and one trial that enrolled patients with an EF less than or equal to 40%. Recognizing these inconsistencies, this Guideline Writing Committee decided to construct recommendations to apply to patients with an EF less than or equal to a range of values. The highest appropriate class of recommendation was then based on all trials that recruited patients with EFs within this range. In this way, potential conflicts between guidelines were reduced and errors due to drawing false conclusions relating to unstudied patient groups were minimized.

Although this led to consistent recommendations, data relating to that range of 35–40% in post-infarction patients is very sparse and relates only to those also with nonsustained ventricular tachycardia. Since these guidelines were published the recommendation of ICD implantation in post-MI patients with an EF <30–40% have generally been translated into ICD implantation in patients post MI patients with EF <30–35% [Level of Evidence

Table 17.2 ICD Indications – comparison between guidelines

Group of patients	ACC/AHA HF 2005 update	ESC HF 2005	ACC/AHA STEMI 2004	ACC/AHA/ NASPE for PM and ICD 2002	ACC/AHA/ESC ventricular arrhythmias and sudden cardiac death 2006
s/p MI, EF ≤ 30%, NYHA II, III	Class I, LOE B	Class IIb, LOE B	Class IIa, LOE B	Class IIa, LOE B	**s/p MI EF = 30–40%***
s/p MI, EF 30–35%, NYHA II, III	Class IIa, LOE B	Class I, LOE A	Class IIa, LOE B	N/A	**NYHA II–III Class I**
s/p MI, EF 30–40%, NSVT, positive EPS	N/A	N/A	Class I, LOE B	Class IIb, LOE B	**LOE A**
s/p MI, EF ≤ 30%, NYHA I	Class IIa, LOE B	N/A	N/A	N/A	**s/p MI, EF = 30–35% NYHA I Class IIa; LOE B**
NICM, EF ≤ 30%, NYHA II, III	Class I, LOE B	Class I, LOE A	N/A	N/A	**LVEF = 30–35% NYHA II-III Class I**
NICM, EF 30–35%, NYHA II, III	Class IIa, LOE B	Class I, LOE A	N/A	N/A	**LOE B**
NICM, EF ≤ 30%, NYHA I	Class IIb, LOE C	N/A	N/A	N/A	**EF = 30–35% Class IIb; LOE C**

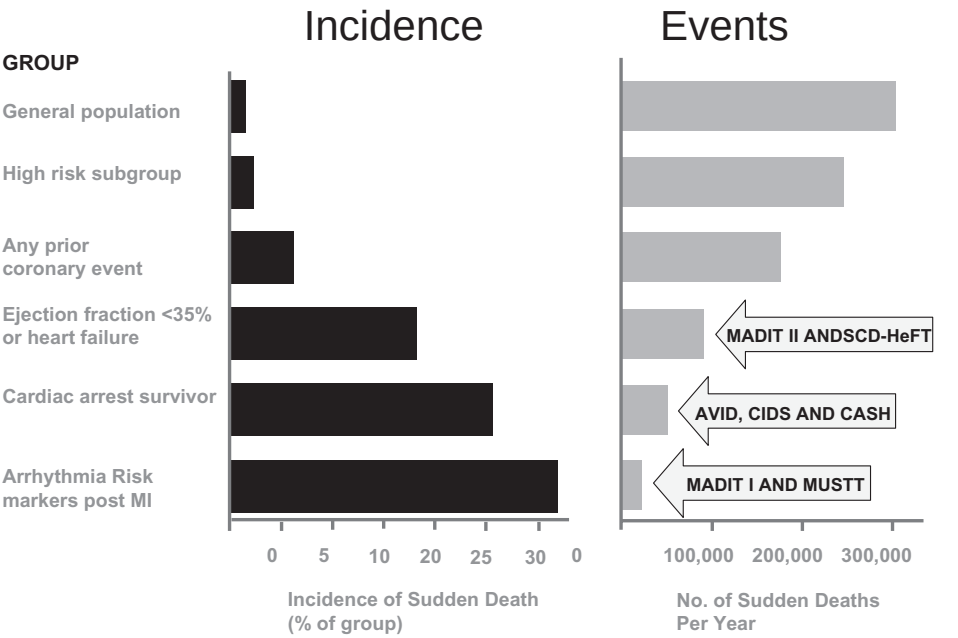
(LOE): A] plus ICD implantation in post-infarct patients with nonsustained ventricular tachycardia and EF = 35–40% [Level of Evidence (LOE): B]. The guideline may be upgraded shortly.

At the time that the guidelines were written there was accumulating good quality evidence that microvolt T wave alternans might be a good predictor of sudden death and the need for ICD therapy. The application of this diagnostic technique was therefore accorded a class IIa, level of evidence – a recommendation for the identification of subjects at risk of sudden cardiac death. Subsequently, however, several new trials have been published which do not support this conclusion and this aspect of the guideline may be upgraded shortly.

These guidelines are concerned with the identification of persons at risk of sudden cardiac death or those suffering from ventricular arrhythmias. The majority of the latter present with symptoms ranging from palpitations to sudden death (Table 17.3), although some with slower and shorter episodes of arrhythmia may be asymptomatic. The identification of patients at risk of

Table 17.3 Clinical presentations of patients with ventricular arrhythmias and sudden cardiac death

- Asymptomatic individuals with or without electrocardiographic abnormalities
- Persons with symptoms potentially attributable to ventricular arrhythmias
  - Palpitations
  - Dyspnea
  - Chest pain
  - Syncope and presyncope
- Ventricular tachycardia that is hemodynamically stable
- Ventricular tachycardia that is not hemodynamically stable
- Cardiac arrest
  - Asystolic (sinus arrest, atrioventricular block)
  - Ventricular tachycardia
  - Ventricular fibrillation
  - Pulseless electrical activity



Myerburg RJ. *Circulation*.1998;97:1514-1521.

Fig. 17.1 Absolute numbers of events and event rates of SCD in the general population and in specific subpopulations over 1 year. General population refers to unselected population age greater than or equal to 35 years, and high-risk subgroups to those with multiple risk factors for a first coronary event. Clinical trials that include specific subpopulations of patients are shown in the right side of the figure. AVID, Antiarrhythmics Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; EF, ejection fraction; HF, heart failure; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter UnSustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial. Redrawn from Myerburg RJ, Kessler KM, Castellanos A. SCD. Structure, function, and time-dependence of risk. Circulation. 1992;85:12–10.

sudden death, other than those who present with arrhythmia usually depends on their suffering other symptoms related to their underlying pathology or they may have the good fortune to be identified by chance when examined or investigated for occupational, pre-operative, or insurance purposes. By far the majority of sudden cardiac death incidents occur in victims who have never presented to a physician with any relevant illness or chance circumstance that allows their risk to be detected [9] (Fig. 17.1).

Noninvasive evaluation

Resting electrocardiogram

Recommendations

Class I

Resting 12-lead ECG is indicated in all patients who are evaluated for ventricular arrhythmias. *(Level of Evidence: A)*

Exercise testing

Recommendations

Class I

1 Exercise testing is recommended in adult patients with ventricular arrhythmias who have an intermediate or greater probability of having CHD by age, gender, and symptoms to provoke ischemic changes or ventricular arrhythmias. *(Level of Evidence: B)*

2 Exercise testing, regardless of age, is useful in patients with known or suspected exercise-induced ventricular arrhythmias, including catecholaminergic VT, to provoke the arrhythmia, achieve a diagnosis, and determine the patient's response to tachycardia. *(Level of Evidence: B)*

Class IIa

Exercise testing can be useful in evaluating response to medical or ablation therapy in patients with

known exercise-induced ventricular arrhythmias. *(Level of Evidence: B)*

Class IIb

1 Exercise testing may be useful in patients with ventricular arrhythmias and a low probability of CHD by age, gender, and symptoms. *(Level of Evidence: C)*

2 Exercise testing may be useful in the investigation of isolated premature ventricular complexes (PVCs) in middle-aged or older patients without other evidence of CHD. *(Level of Evidence: C)*

Ambulatory electrocardiography

Recommendations

Class I

1 Ambulatory ECG is indicated when there is a need to clarify the diagnosis by detecting arrhythmias, QT-interval changes, T-wave alternans (TWA), or ST changes, to evaluate risk, or to judge therapy. *(Level of Evidence: A)*

2 Event monitors are indicated when symptoms are sporadic to establish whether or not they are caused by transient arrhythmias. *(Level of Evidence: B)*

3 Implantable recorders are useful in patients with sporadic symptoms suspected to be related to arrhythmias such as syncope when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques. *(Level of Evidence: B)*

Electrocardiographic techniques and measurements

Recommendations

Class IIa

It is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias. *(Level of Evidence: A)* [10,11]

Class IIb

ECG techniques such as signal-averaged ECG (SAECG), heart rate variability (HRV), baroreflex sensitivity, and heart rate turbulence may be useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias. *(Level of Evidence: B)*

Left ventricular function and imaging

Recommendations

Class I

1 Echocardiography is recommended in patients with ventricular arrhythmias who are suspected of having structural heart disease. *(Level of Evidence: B)*

2 Echocardiography is recommended for the subset of patients at high risk for the development of serious ventricular arrhythmias or SCD, such as those with dilated, hypertrophic, or RV cardiomyopathies, AMI survivors, or relatives of patients with inherited disorders associated with SCD. *(Level of Evidence: B)*

3 Exercise testing with an imaging modality (echocardiography or nuclear perfusion [single-photon emission computed tomography (SPECT)]) is recommended to detect silent ischemia in patients with ventricular arrhythmias who have an intermediate probability of having CHD by age, symptoms, and gender and in whom ECG assessment is less reliable because of digoxin use, LVH, greater than 1 mm ST-segment depression at rest, WPW syndrome, or LBBB. *(Level of Evidence: B)*

4 Pharmacological stress testing with an imaging modality (echocardiography or myocardial perfusion SPECT) is recommended to detect silent ischemia in patients with ventricular arrhythmias who have an intermediate probability of having CHD by age, symptoms, and gender and are physically unable to perform a symptom limited exercise test. *(Level of Evidence: B)*

Class IIa

1 MRI, cardiac computed tomography (CT), or radionuclide angiography can be useful in patients with ventricular arrhythmias when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes. *(Level of Evidence: B)*

2 Coronary angiography can be useful in establishing or excluding the presence of significant obstructive CHD in patients with life-threatening ventricular arrhythmias or in survivors of SCD, who have an intermediate or greater probability of having CHD by age, symptoms, and gender. *(Level of Evidence: C)*

3 LF imaging can be useful in patients undergoing biventricular pacing. *(Level of Evidence: C)*

Electrophysiological testing

Recommendations

Class I

1 EP testing is recommended for diagnostic evaluation of patients with remote MI with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope, and syncope. *(Level of Evidence: B)*

2 EP testing is recommended in patients with CHD to guide and assess the efficacy of VT ablation. *(Level of Evidence: B)*

3 EP testing is useful in patients with CHD for the diagnostic evaluation of wide-QRS-complex tachycardias of unclear mechanism. *(Level of Evidence: C)*

Class IIa

EP testing is reasonable for risk stratification in patients with remote MI, NSVT, and LVEF equal to or less than 40%. *(Level of Evidence: B)*

Electrophysiological testing in patients with syncope

Recommendations

Class I

EP testing is recommended in patients with syncope of unknown cause with impaired LV function or structural heart disease. *(Level of Evidence: B)*

Class IIa

EP testing can be useful in patients with syncope when bradyarrhythmias or tachyarrhythmias are suspected and in whom noninvasive diagnostic studies are not conclusive. *(Level of Evidence: B)*

Ablation [12,13]

Recommendations

Class I

1 Ablation is indicated in patients who are otherwise at low risk for SCD and have sustained predominantly monomorphic VT that is drug resistant, who are drug intolerant, or who do not wish long-term drug therapy. *(Level of Evidence: C)*

2 Ablation is indicated in patients with bundle-branch re-entrant VT. *(Level of Evidence: C)*

3 Ablation is indicated as adjunctive therapy in patients with an ICD who are receiving multiple shocks as a result of sustained VT that is not manageable by reprogramming or changing drug therapy or who do not wish long-term drug therapy. *(Level of Evidence: C)*

4 Ablation is indicated in patients with WPW syndrome resuscitated from sudden cardiac arrest due to AF and rapid conduction over the accessory pathway causing VF. *(Level of Evidence: B)*

Class IIa

1 Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have symptomatic nonsustained monomorphic VT that is drug resistant, who are drug intolerant or who do not wish long-term drug therapy. *(Level of Evidence: C)*

2 Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have frequent symptomatic predominantly monomorphic PVCs that are drug resistant or who are drug intolerant or who do not wish long-term drug therapy. *(Level of Evidence: C)*

3 Ablation can be useful in symptomatic patients with WPW syndrome who have accessory pathways with refractory periods less than 240 ms in duration. *(Level of Evidence: B)*

Class IIb

1 Ablation of Purkinje fiber potentials may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology. *(Level of Evidence: C)*

2 Ablation of asymptomatic PVCs may be considered when the PVCs are very frequent to avoid or treat tachycardia-induced cardiomyopathy. *(Level of Evidence: C)*

Class III

Ablation of asymptomatic relatively infrequent PVCs is not indicated. *(Level of Evidence: C)*

Acute management of specific arrhythmias

Management of cardiac arrest [14,15]

Recommendations

Class I

1 After establishing the presence of definite, suspected, or impending cardiac arrest, the first priority should be activation of a response team capable of identifying the specific mechanism and carrying out prompt intervention. *(Level of Evidence: B)*

2 Cardiopulmonary resuscitation (CPR) should be implemented immediately after contacting a response team. *(Level of Evidence: A)*
3 In an out-of-hospital setting, if an AED is available, it should be applied immediately and shock therapy administered according to the algorithms contained in the documents on CPR developed by the AHA in association with the International Liaison Committee on Resuscitation (ILCOR) and/or the European Resuscitation Council (ERC). *(Level of Evidence: C)*
4 For victims with ventricular tachyarrhythmic mechanisms of cardiac arrest, when recurrences occur after a maximally defibrillating shock (generally 360 J for monophasic defibrillators), intravenous amiodarone should be the preferred antiarrhythmic drug for attempting a stable rhythm after further defibrillations. *(Level of Evidence: B)*
5 For recurrent ventricular tachyarrhythmias or nontachyarrhythmic mechanisms of cardiac arrest, it is recommended to follow the algorithms contained in the documents on CPR developed by the AHA in association with ILCOR and/or the ERC. *(Level of Evidence: C)*
6 Reversible causes and factors contributing to cardiac arrest should be managed during advanced life support, including management of hypoxia, electrolyte disturbances, mechanical factors, and volume depletion. *(Level of Evidence: C)*

Class IIa

For response times greater than or equal to 5 min, a brief (less than 90 to 180 s) period of CPR is reasonable prior to attempting defibrillation. *(Level of Evidence: B)*

Class IIb

A single precordial thump may be considered by health care professional providers when responding to a witnessed cardiac arrest. *(Level of Evidence: C)*

Ventricular tachycardia associated with low troponin myocardial infarction

Recommendations

Class I

Patients presenting with sustained VT in whom low level elevations in cardiac biomarkers of myocyte injury/necrosis are documented should be treated similarly to patients who have sustained VT and in whom no biomarker rise is documented. *(Level of Evidence: C)*

Sustained monomorphic ventricular tachycardia

Recommendations

Class I

1 Wide-QRS tachycardia should be presumed to be VT if the diagnosis is unclear. *(Level of Evidence: C)*
2 Direct current cardioversion with appropriate sedation is recommended at any point in the treatment cascade in patients with suspected sustained monomorphic VT with hemodynamic compromise. *(Level of Evidence: C)*

Class IIa

1 Intravenous procainamide (or ajmaline in some European countries) is reasonable for initial treatment of patients with stable sustained monomorphic VT. *(Level of Evidence: B)*
2 Intravenous amiodarone is reasonable in patients with sustained monomorphic VT that is hemodynamically unstable, refractory to conversion with counter-shock, or recurrent despite procainamide or other agents. *(Level of Evidence: C)*
3 Transvenous catheter pace termination can be useful to treat patients with sustained monomorphic VT that is refractory to cardioversion or is frequently recurrent despite antiarrhythmic medication. *(Level of Evidence: C)*

Class IIb

Intravenous lidocaine might be reasonable for the initial treatment of patients with stable sustained monomorphic VT specifically associated with acute myocardial ischemia or infarction. *(Level of Evidence: C)*

Class III

Calcium channel blockers such as verapamil and diltiazem should not be used in patients to terminate wide-QRS-complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction. *(Level of Evidence: C)*

Repetitive monomorphic ventricular tachycardia

Recommendations

Class IIa

Intravenous amiodarone, beta-blockers, and intravenous procainamide (or sotalol or ajmaline in

Europe) can be useful for treating repetitive monomorphic VT in the context of coronary disease and idiopathic VT. *(Level of Evidence: C)*

Polymorphic VT

Recommendations

Class I

1 Direct current cardioversion with appropriate sedation as necessary is recommended for patients with sustained polymorphic VT with hemodynamic compromise and is reasonable at any point in the treatment cascade. *(Level of Evidence: B)*

2 Intravenous beta-blockers are useful for patients with recurrent polymorphic VT, especially if ischemia is suspected or cannot be excluded. *(Level of Evidence: B)*

3 Intravenous loading with amiodarone is useful for patients with recurrent polymorphic VT in the absence of abnormal repolarization related to congenital or acquired LQTS. *(Level of Evidence: C)*

4 Urgent angiography with a view to revascularization should be considered for patients with polymorphic VT when myocardial ischemia cannot be excluded. *(Level of Evidence: C)*

Class IIb

Intravenous lidocaine may be reasonable for treatment of polymorphic VT specifically associated with acute myocardial ischemia or infarction. *(Level of Evidence: C)*

Torsades de pointes

Recommendations

Class I

1 Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with torsades de pointes. *(Level of Evidence: A)*

2 Acute and long-term pacing is recommended for patients presenting with torsades de pointes due to heart block and symptomatic bradycardia. *(Level of Evidence: A)*

Class IIa

1 Management with intravenous magnesium sulfate is reasonable for patients who present with LQTS and few episodes of torsades de pointes. Magnesium is not likely to be effective in patients with a normal QT interval. *(Level of Evidence: B)*

2 Acute and long-term pacing is reasonable for patients who present with recurrent pause-dependent torsades de pointes. *(Level of Evidence: B)*

3 Beta-blockade combined with pacing is reasonable acute therapy for patients who present with torsades de pointes and sinus bradycardia. *(Level of Evidence: C)*

4 Isoproterenol is reasonable as temporary treatment in acute patients who present with recurrent pause dependent torsades de pointes who do not have congenital LQTS. *(Level of Evidence: B)*

Class IIb

1 Potassium repletion to 4.5 to 5 mmol/L may be considered for patients who present with torsades de pointes. *(Level of Evidence: B)*

2 Intravenous lidocaine or oral mexiletine may be considered in patients who present with LQT3 and torsades de pointes. *(Level of Evidence: C)*

Incessant ventricular tachycardia

Recommendations

Class I

Revascularization and beta-blockade followed by intravenous antiarrhythmic drugs such as procainamide or amiodarone are recommended for patients with recurrent or incessant polymorphic VT due to acute myocardial ischemia. *(Level of Evidence: C)*

Class IIa

Intravenous amiodarone or procainamide followed by VT ablation can be effective in the management of patients with frequently recurring or incessant monomorphic VT. *(Level of Evidence: B)*

Class IIb

1 Intravenous amiodarone and intravenous beta-blockers separately or together may be reasonable in patients with VT storm. *(Level of Evidence: C)*

2 Overdrive pacing or general anesthesia may be considered for patients with frequently recurring or incessant VT. *(Level of Evidence: C)*

3 Spinal cord modulation may be considered for some patients with frequently recurring or incessant VT. *(Level of Evidence: C)*

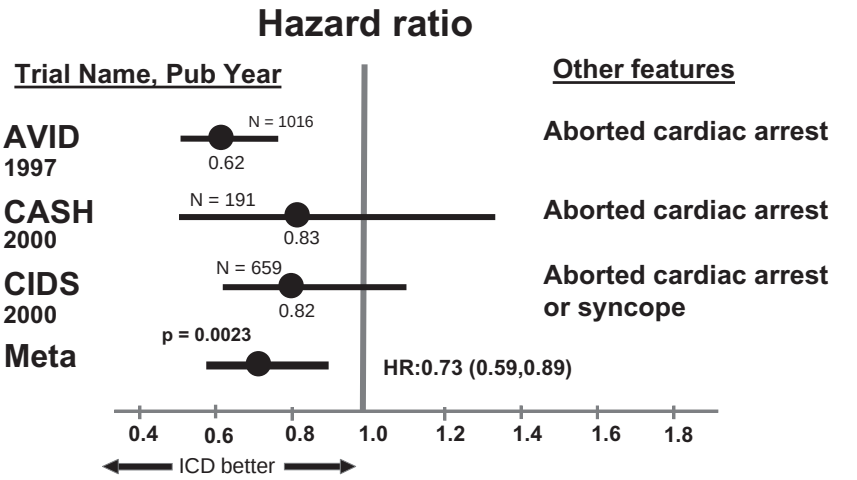


Fig. 17.2 Summary of the results of secondary prevention ICD trials The hazard ratio for the three individual trials and the meta analysis are plotted. AVID, Antiarrhythmics Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; meta, meta-analysis reported by Connelly *et al.*

Ventricular arrhythmia and sudden cardiac death related to specific pathology

Left ventricular dysfunction due to prior myocardial infarction

Recommendations

Class I

1 Aggressive attempts should be made to treat HF that may be present in some patients with LV dysfunction due to prior MI and ventricular tachyarrhythmias. *(Level of Evidence: C)*

2 Aggressive attempts should be made to treat myocardial ischemia that may be present in some patients with ventricular tachyarrhythmias. *(Level of Evidence: C)*

3 Coronary revascularization is indicated to reduce the risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischemia is documented to immediately precede the onset of VF. *(Level of Evidence: B)*

4 If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Fig. 17.2).

5 ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30% to 40% are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Figs 17.3–17.5; Table 17.4) [16–25].

6 The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with hemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Fig. 17.2) [26–29].

Class IIa

1 Implantation of an ICD is reasonable in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)* (Fig. 17.3).

2 Amiodarone, often in combination with beta-blockers, can be useful for patients with LV

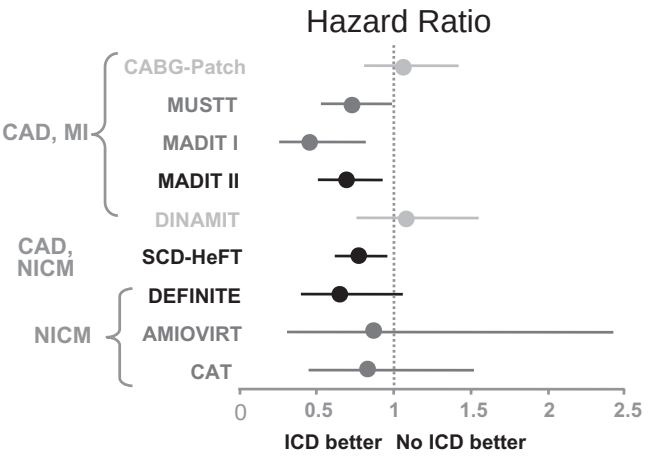


Fig. 17.3 Plot of hazard ratios and confidence intervals in the primary prevention ICD trials. CABG-Patch, Coronary Artery Bypass Graft Patch Trial, MADIT, Multicenter Automatic Defibrillator Implantation Trial, MUSTT, Multicenter UnSustained Tachycardia Trial, DINAMIT, Defibrillator in Acute Myocardial Infarction Trial, SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial, DEFINITE, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation, AMIOVERT, Amiodarone Versus Implantable Cardioverter-Defibrillator, CAT, Cardiomyopathy Trial.

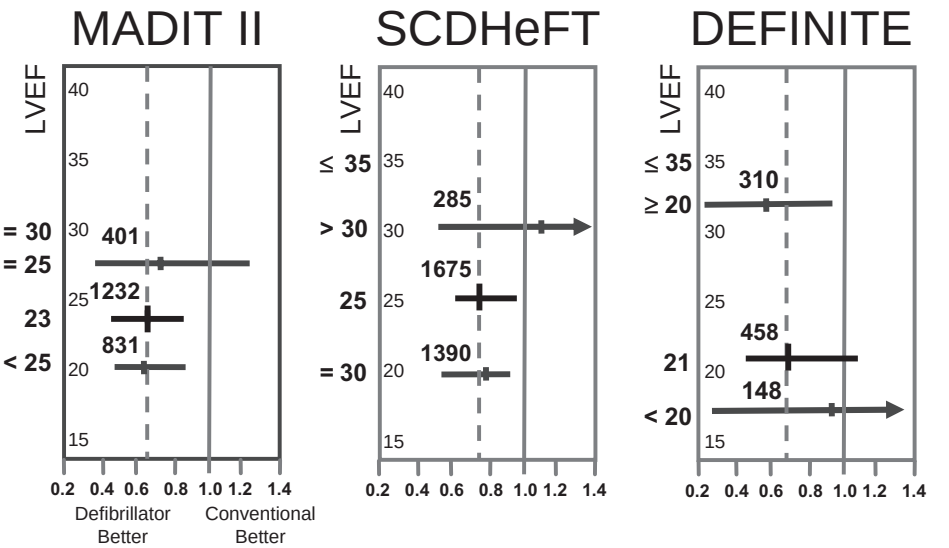


Fig. 17.4 Summary of the three main ICD primary prevention trials: MADIT II, Multicenter Automatic Defibrillator Implantation Trial II, SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial and DEFINITE, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation. The dark bars are the main trial result (hazard ratio and 95% confidence intervals plotted against the mean left ventricular ejection fraction (LVEF) in the trial. The dotted horizontal line is the LVEF at or below which patients could be recruited into the trial. The gray bars are results reported by the trial investigators for subgroups within the specified LVEF ranges.

dysfunction due to prior MI and symptoms due to VT unresponsive to beta-adrenergic-blocking agents. *(Level of Evidence: B)* (Fig. 17.6) [30–33].

3 Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LV dysfunction due to prior MI unresponsive to beta-blocking agents. *(Level of Evidence: C)*

4 Adjunctive therapies to the ICD, including catheter ablation or surgical resection, and pharmaco-

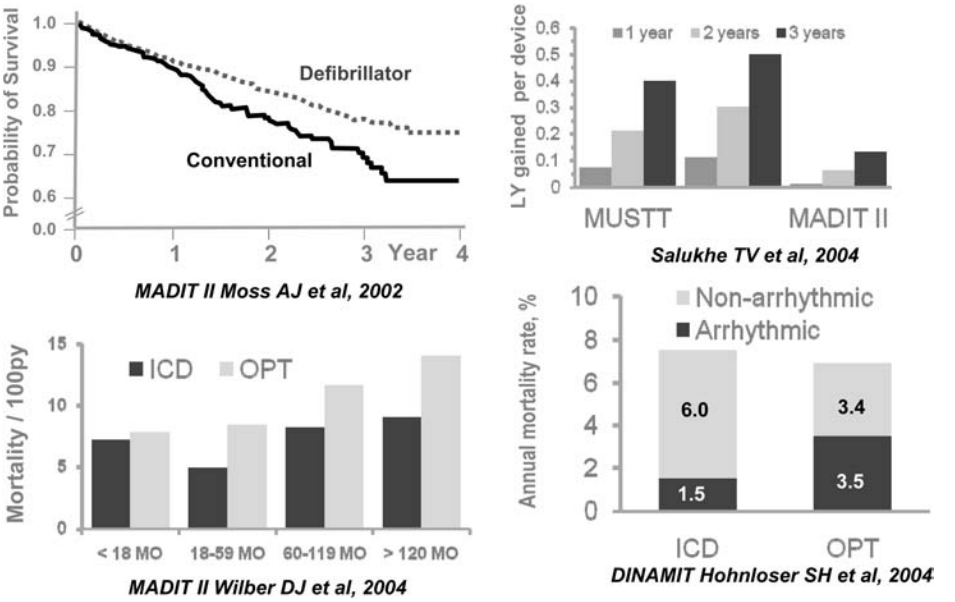


Fig. 17.5 Some trial results and analyses which bear on the restriction of ICD indication to a period later than 40 days after acute myocardial infarction in patients who have a life expectancy of at least 1 year: (1) MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) results suggest that benefit from the ICD is gained only after about 12 months of follow-up (top left) and (2) those who most benefit were recruited to the trial more than 18 months following their index myocardial infarction (bottom left); (3) substantially greater life year gains are seen when patients from MADIT or MUSTT (Multicenter UnSustained Tachycardia Trial) are followed for longer periods after myocardial infarction (top right); and (4) recruitment of patients shortly after myocardial infarction (within 40 days) is not associated with any net benefit according to the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) because the reduction in arrhythmic mortality is more than offset by increased nonarrhythmic mortality in the ICD treated group.

Table 17.4 Major ICD Secondary Prevention Trials

Study	MADIT II	DEFINITE	SCD HeFT
Sponsor	Guidant	St Jude	MIH/Wyeth/Medtronic
Reported in NEJM	Mar 2002	May 2004	Jan 2005
No of patients	1232	458	2521
Disease	MI	CM/CHF	CHF
NYHA I/II/III/IV	37/34.5/24/4.5	21.6/57.4/21.0/. . .	. . ./70/30/. . .
LVEF, %	≤30 (23)	≤35 (21)	≤35 (25)
IHD/NIHD, %	100/. . .	. . ./100	52/48
Device	ICD	ICD	ICD
1° end-point	ACM	ACM	ACM
Study duration	Jul 1997–Nov 2001	July 1998–June 2002	Sep 1997–Jul 2001
Follow-up, months	20	29	45.5

logical therapy with agents such as amiodarone or sotalol are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI. *(Level of Evidence: C)* [34].

5 Amiodarone is reasonable therapy to reduce symptoms due to recurrent hemodynamically stable VT for patients with LV dysfunction due to prior MI who cannot or refuse to have an ICD implanted. *(Level of Evidence: C)*

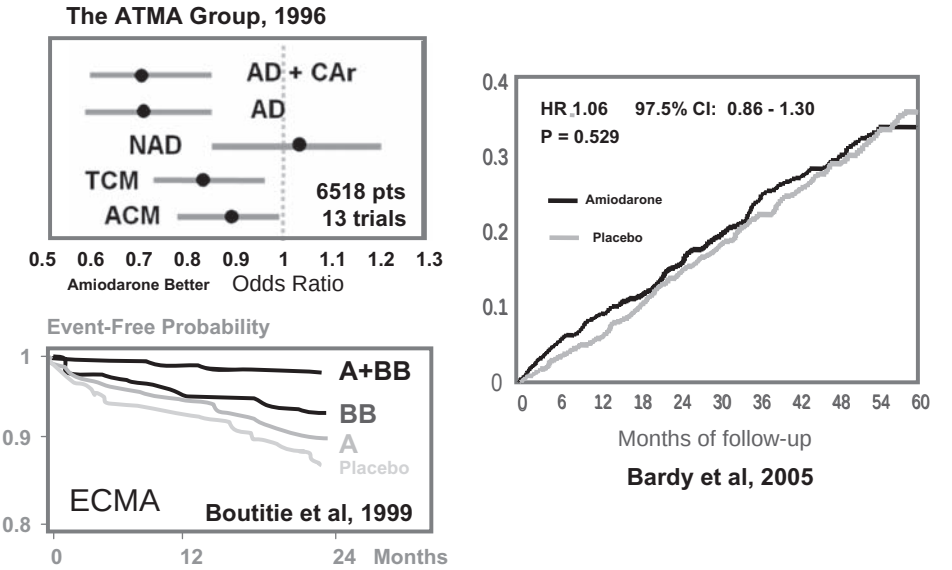


Fig. 17.6 Pictorial representation of the controversy related to the possible value of amiodarone for the prevention of sudden cardiac death in patients with heart failure or recent myocardial infarction. The ATMA, Amiodarone Trial Meta Analysis, and ECMA, EMIAT, European Myocardial Infarction Amiodarone Trial, and CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) Meta Analyses demonstrated benefit from amiodarone particularly when combined with beta-blockade. SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial, however, demonstrated no difference between amiodarone and placebo treatment for patients with NYHA Class II or III heart failure and an ejection fraction ≤35%. A, amiodarone; BB, beta-blockade; AD, arrhythmic death; CAr, cardiac arrest; NAD, nonarrhythmic death; TCM, total cardiac mortality; ACM, all cause mortality; pts, patients; HR, hazard ratio; CI, confidence interval.

6 Implantation is reasonable for treatment of recurrent ventricular tachycardia in patients post-MI with normal or near normal ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIb

1 Curative catheter ablation or amiodarone may be considered in lieu of ICD therapy to improve symptoms in patients with LV dysfunction due to prior MI and recurrent hemodynamically stable VT whose LVEF is greater than 40%. *(Level of Evidence: B)* (Fig. 17.6) [33].

2 Amiodarone may be reasonable therapy for patients with LV dysfunction due to prior MI with an ICD indication, as defined above, in patients who cannot or refuse to have an ICD implanted. *(Level of Evidence: C)* (Fig. 17.6) [33].

Class III

1 Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. *(Level of Evidence: B)*

2 Class IC antiarrhythmic drugs in patients with a past history of MI should not be used. *(Level of Evidence: A)*

Valvular heart disease

Recommendations

Class I

Patients with valvular heart disease and ventricular arrhythmias should be evaluated and treated following current recommendations for each disorder. *(Level of Evidence: C)*

Class IIb

The effectiveness of mitral valve repair or replacement to reduce the risk of SCD in patients with mitral valve prolapse, severe mitral regurgitation,

and serious ventricular arrhythmias is not well established. *(Level of Evidence: C)*

Congenital heart disease

Recommendations

Class I

1 ICD implantation is indicated in patients with congenital heart disease who are survivors of cardiac arrest after evaluation to define the cause of the event and exclude any reversible causes. ICD implantation is indicated in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

2 Patients with congenital heart disease and spontaneous sustained VT should undergo invasive hemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended. *(Level of Evidence: C)*

Class IIa

Invasive hemodynamic and EP evaluation is reasonable in patients with congenital heart disease and unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIb

EP testing may be considered for patients with congenital heart disease and ventricular couplets or NSVT to determine the risk of a sustained ventricular arrhythmia. *(Level of Evidence: C)*

Class III

Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated PVCs. *(Level of Evidence: C)*

Myocarditis, rheumatic disease, and endocarditis

Recommendations

Class I

1 Temporary pacemaker insertion is indicated in patients with symptomatic bradycardia and/or heart block during the acute phase of myocarditis. *(Level of Evidence: C)*

2 Acute aortic regurgitation associated with VT should be treated surgically unless otherwise contraindicated. *(Level of Evidence: C)*

3 Acute endocarditis complicated by aortic or annular abscess and AV block should be treated surgically unless otherwise contraindicated. *(Level of Evidence: C)*

Class IIa

1 ICD implantation can be beneficial in patients with life-threatening ventricular arrhythmias who are not in the acute phase of myocarditis, as indicated in the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

2 Antiarrhythmic therapy can be useful in patients with symptomatic NSVT or sustained VT during the acute phase of myocarditis. *(Level of Evidence: C)*

Class III

ICD implantation is not indicated during the acute phase of myocarditis. *(Level of Evidence: C)*

Infiltrative cardiomyopathies

Recommendations

Class I

In addition to managing the underlying infiltrative cardiomyopathy, life-threatening arrhythmias should be treated in the same manner that such arrhythmias are treated in patients with other cardiomyopathies, including the use of ICD and pacemakers in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Endocrine disorders and diabetes

Recommendations

Class I

1 The management of ventricular arrhythmias secondary to endocrine disorders should address the electrolyte (potassium, magnesium, and calcium) imbalance and the treatment of the underlying endocrinopathy. *(Level of Evidence: C)*

2 Persistent life-threatening ventricular arrhythmias that develop in patients with endocrine disorders should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including use of ICD and pacemaker implantation as required in those who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

3 Patients with diabetes with ventricular arrhythmias should generally be treated in the same manner as patients without diabetes. *(Level of Evidence: A)*

End-stage renal failure

Recommendations

Class I

1 The acute management of ventricular arrhythmias in end-stage renal failure should immediately address hemodynamic status and electrolyte (potassium, magnesium, and calcium) imbalance. *(Level of Evidence: C)*

2 Life-threatening ventricular arrhythmias, especially in patients awaiting renal transplantation, should be treated conventionally, including the use of ICD and pacemaker as required, in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Obesity, dieting, and anorexia

Recommendations

Class I

Life-threatening ventricular arrhythmias in patients with obesity, anorexia, or when dieting should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including ICD and pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIa

Programmed weight reduction in obesity and carefully controlled re-feeding in anorexia can effectively reduce the risk of ventricular arrhythmias and SCD. *(Level of Evidence: C)*

Class III

Prolonged, unbalanced, very low calorie, semi-starvation diets are not recommended; they may be harmful and provoke life-threatening ventricular arrhythmias. *(Level of Evidence: C)*

Pulmonary arterial hypertension

Recommendations

Class III

Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension (PAH) or other pulmonary conditions. *(Level of Evidence: C)*

Transient arrhythmias of reversible cause

Recommendations

Class I

1 Myocardial revascularization should be performed, when appropriate, to reduce the risk of SCD in patients experiencing cardiac arrest due to VF or polymorphic VT in the setting of acute ischemia or MI. *(Level of Evidence: C)*

2 Unless electrolyte abnormalities are proved to be the cause, survivors of cardiac arrest due to VF or polymorphic VT in whom electrolyte abnormalities are discovered in general should be evaluated and treated in a manner similar to that of cardiac arrest without electrolyte abnormalities. *(Level of Evidence: C)*

3 Patients who experience sustained monomorphic VT in the presence of antiarrhythmic drugs or electrolyte abnormalities should be evaluated and treated in a manner similar to that of patients with VT without electrolyte abnormalities or antiarrhythmic drugs present. Antiarrhythmic drugs or electrolyte abnormalities should not be assumed to be the sole cause of sustained monomorphic VT. *(Level of Evidence: B)*

4 Patients who experience polymorphic VT in association with prolonged QT interval due to antiarrhythmic medications or other drugs should be advised to avoid exposure to all agents associated with QT prolongation. A list of such drugs can be found on the Web sites www.qtdrugs.org and www.torsades.org *(Level of Evidence: B)*

Ventricular arrhythmias associated with cardiomyopathies

Dilated cardiomyopathy (nonischemic) [35–38]

Recommendations

Class I

1 EP testing is useful to diagnose bundle-branch re-entrant tachycardia and to guide ablation in patients with nonischemic DCM. *(Level of Evidence: C)*

2 EP testing is useful for diagnostic evaluation in patients with nonischemic DCM with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope. *(Level of Evidence: C)*

3 An ICD should be implanted in patients with nonischemic DCM and significant LV dysfunction who have sustained VT or VF, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Fig. 17.2)

4 ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic DCM who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)* (Figs 17.3 and 17.4; Table 17.4).

Class IIa

1 ICD implantation can be beneficial for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)* (Fig. 17.2).

2 ICD implantation can be effective for termination of sustained VT in patients with normal or near normal ventricular function and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIb

1 Amiodarone may be considered for sustained VT or VF in patients with nonischemic DCM. *(Level of Evidence: C)*

2 Placement of an ICD might be considered in patients who have nonischemic DCM, LVEF of less than or equal to 30% to 35%, who are NYHA functional class I receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Hypertrophic cardiomyopathy [39–43]

Recommendations

Class I

ICD therapy should be used for treatment in patients with HCM who have sustained VT and/or VF and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIa

1 ICD implantation can be effective for primary prophylaxis against SCD in patients with HCM who have 1 or more major risk factor (Table 17.5) for SCD and who are receiving chronic optimal medical therapy and in patients who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

2 Amiodarone therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when an ICD is not feasible. *(Level of Evidence: C)*

Class IIb

1 EP testing may be considered for risk assessment for SCD in patients with HCM. *(Level of Evidence: C)*

2 Amiodarone may be considered for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor for SCD (see Table 17.6) if ICD implantation is not feasible. *(Level of Evidence: C)*

Arrhythmogenic right ventricular cardiomyopathy [44–45]

Recommendations

Class I

ICD implantation is recommended for the prevention of SCD in patients with ARVC with

Table 17.5 Risk factors for sudden cardiac death in hypertrophic cardiomyopathy

Major risk factor	Possible in individual patients
Cardiac arrest (VF)	Atrial fibrillation
Spontaneous sustained VT	Myocardial ischemia
Family history of premature sudden death	LV outflow obstruction
Unexplained syncope	High risk mutation
LV thickness ≥30 mm	Intense (competititve) physical exertion
Abnormal exercise BP	
Non-sustained spontaneous VT	

AF, atrial fibrillation; BP, blood pressure; LV, left ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia. Modified with permission from Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.

documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIa

1 ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, one or more affected family member with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

2 Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with ARVC when ICD implantation is not feasible. *(Level of Evidence: C)*

3 Ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent VT, despite optimal antiarrhythmic drug therapy. *(Level of Evidence: C)*

Class IIb

EP testing might be useful for risk assessment of SCD in patients with ARVC. *(Level of Evidence: C)*

Neuromuscular disorders

Recommendations

Class I

Patients with neuromuscular disorders who have ventricular arrhythmias should generally be treated in the same manner as patients without neuromuscular disorders. *(Level of Evidence: A)*

Class IIb

Permanent pacemaker insertion may be considered for neuromuscular diseases such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AV block (including first-degree AV block) with or without symptoms, because there may be unpredictable progression of AV conduction disease. *(Level of Evidence: B)*

Heart failure

Recommendations

Class I

1 ICD therapy is recommended for secondary prevention of SCD in patients who survived VF or hemodynamically unstable VT, or VT with syncope and who have an LVEF less than or equal to 40%, who are receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Fig. 17.2) [26–29].

2 ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)* (Figs 17.3 and 17.4; Table 17.4) [18–24,35–38].

3 ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)* (Figs 17.3 and 17.4; Table 17.4).

4 Amiodarone, sotalol, and/or other beta-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with HF. *(Level of Evidence: C)* [33–34].

5 Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. *(Level of Evidence: B)*

Class IIa

1 ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD in patients with NYHA functional class III or IV, are receiving optimal medical therapy, in sinus rhythm with a QRS complex of at least 120 msec, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

2 ICD therapy is reasonable for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

3 ICD therapy is reasonable in patients who have recurrent stable VT, a normal or near normal LVEF, and optimally treated HF and who have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

4 Biventricular pacing in the absence of ICD therapy is reasonable for the prevention of SCD in patients with NYHA functional class III or IV HF, an LVEF less than or equal to 35%, and a QRS complex equal to or wider than 160 msec (or at least 120 msec in the presence of other evidence of ventricular dyssynchrony) who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIb

1 Amiodarone, sotalol, and/or beta-blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible. *(Level of Evidence: C)* (Fig. 17.6).

2 ICD therapy may be considered for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Genetic arrhythmia syndromes

Long QT syndrome [46–48]

Recommendations

Class I

1 Lifestyle modification is recommended for patients with an LQTS diagnosis (clinical and/or molecular). *(Level of Evidence: B)*

2 Beta-blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). *(Level of Evidence: B)*

3 Implantation of an ICD along with use of beta-blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*

Class IIa

1 Beta-blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. *(Level of Evidence: B)*

2 Implantation of an ICD with continued use of beta-blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT

while receiving beta-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Class IIb

1 Left cardiac sympathetic neural denervation may be considered for LQTS patients with syncope, torsades de pointes, or cardiac arrest while receiving beta-blockers. *(Level of Evidence: B)*

2 Implantation of an ICD with the use of beta-blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

Brugada syndrome [49–52]

Recommendations

Class I

An ICD is indicated for Brugada syndrome patients with previous cardiac arrest receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIa

1 An ICD is reasonable for Brugada syndrome patients with spontaneous ST-segment elevation in V1, V2, or V3 who have had syncope with or without mutations demonstrated in the SCN5A gene and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

2 Clinical monitoring for the development of a spontaneous ST-segment elevation pattern is reasonable for the management of patients with ST-segment elevation induced only with provocative pharmacological challenge with or without symptoms. *(Level of Evidence: C)*

3 An ICD is reasonable for Brugada syndrome patients with documented VT that has not resulted in cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

4 Isoproterenol can be useful to treat an electrical storm in the Brugada syndrome. *(Level of Evidence: C)*

Class IIb

1 EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation with or without a mutation in the SCN5A gene. *(Level of Evidence: C)*

2 Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. *(Level of Evidence: C)*

Catecholaminergic polymorphic ventricular tachycardia

Recommendations

Class I

1 Beta-blockers are indicated for patients who are clinically diagnosed with CPVT on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. *(Level of Evidence: C)*

2 Implantation of an ICD with use of beta-blockers is indicated for patients with CPVT who are survivors of cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIa

1 Beta-blockers can be effective in patients without clinical manifestations when the diagnosis of CPVT is established during childhood based on genetic analysis. *(Level of Evidence: C)*

2 Implantation of an ICD with the use of beta-blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIb

Beta-blockers may be considered for patients with CPVT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. *(Level of Evidence: C)*

Arrhythmias in structurally normal hearts

Idiopathic ventricular tachycardia

Recommendations

Class I

Catheter ablation is useful in patients with structurally normal hearts with symptomatic, drug-

refractory VT arising from the RV or LV or in those who are drug intolerant or who do not desire long-term drug therapy. *(Level of Evidence: C)*

Class IIa

1 EP testing is reasonable for diagnostic evaluation in patients with structurally normal hearts with palpitations or suspected outflow tract VT. *(Level of Evidence: B)*

2 Drug therapy with beta-blockers and/or calcium channel blockers (and/or IC agents in RVOT VT) can be useful in patients with structurally normal hearts with symptomatic VT arising from the RV. *(Level of Evidence: C)*

3 ICD implantation can be effective therapy for the termination of sustained VT in patients with normal or near normal ventricular function and no structural heart disease who are receiving chronic optimal medical therapy and who have reasonable expectation of survival for more than 1 year. *(Level of Evidence: C)*

Electrolyte disturbances

Recommendations

Class I

Potassium (and magnesium) salts are useful in treating ventricular arrhythmias secondary to hypokalemia (or hypomagnesmia) resulting from diuretic use in patients with structurally normal hearts. *(Level of Evidence: B)*

Class IIa

1 It is reasonable to maintain serum potassium levels above 4.0 mM/L in any patient with documented life-threatening ventricular arrhythmias and a structurally normal heart. *(Level of Evidence: C)*

2 It is reasonable to maintain serum potassium levels above 4.0 mM/L in patients with acute MI. *(Level of Evidence: B)*

3 Magnesium salts can be beneficial in the management of VT secondary to digoxin toxicity in patients with structurally normal hearts. *(Level of Evidence: B)*

Alcohol

Recommendations

Class I

1 Complete abstinence from alcohol is recommended in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias. *(Level of Evidence: C)*

2 Persistent life-threatening ventricular arrhythmias despite abstinence from alcohol should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including an ICD, as required, in patients receiving chronic optimal medical therapy and who have reasonable expectation of survival for more than 1 year. *(Level of Evidence: C)*

Smoking

Recommendations

Class I

Smoking should be strongly discouraged in all patients with suspected or documented ventricular arrhythmias and/or aborted SCD. *(Level of Evidence: B)*

Lipids

Recommendations

Class I

Statin therapy is beneficial in patients with CHD to reduce the risk of vascular events, possibly ventricular arrhythmias, and SCD. *(Level of Evidence: A)*

Class IIb

n-3 polyunsaturated fatty acid supplementation may be considered for patients with ventricular arrhythmias and underlying CHD. *(Level of Evidence: B)*

Ventricular arrhythmias and sudden cardiac death related to specific populations

Athletes [53–55]

Recommendations

Class I

1 Preparticipation history and physical examination, including family history of premature or SCD and specific evidence of cardiovascular diseases such as cardiomyopathies and ion channel abnormalities, is recommended in athletes. *(Level of Evidence: C)*

2 Athletes presenting with rhythm disorders, structural heart disease, or other signs or symptoms suspicious for cardiovascular disorders should be evaluated as any other patient but with recognition of the potential uniqueness of their activity. *(Level of Evidence: C)*

3 Athletes presenting with syncope should be carefully evaluated to uncover underlying cardiovascular disease or rhythm disorder. *(Level of Evidence: B)*

4 Athletes with serious symptoms should cease competition while cardiovascular abnormalities are being fully evaluated. *(Level of Evidence: C)*

Class IIb

Twelve-lead ECG and possibly echocardiography may be considered as pre-participation screening for heart disorders in athletes. *(Level of Evidence: B)*

Gender and pregnancy

Recommendations

Class I

1 Pregnant women developing hemodynamically unstable VT or VF should be electrically cardioverted or defibrillated. *(Level of Evidence: B)*

2 In pregnant women with the LQTS who have had symptoms, it is beneficial to continue beta-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. *(Level of Evidence: C)*

Elderly patients

Recommendations

Class I

1 Elderly patients with ventricular arrhythmias should generally be treated in the same manner as younger individuals. *(Level of Evidence: A)*

2 The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients. *(Level of Evidence: C)*

Class III

Elderly patients with projected life expectancy less than 1 year due to major co-morbidities should not receive ICD therapy. *(Level of Evidence: C)*

Pediatric patients

Recommendations

Class I

1 An ICD should be implanted in pediatric survivors of a cardiac arrest when a thorough search for a correctable cause is negative and the patients are receiving optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

2 Hemodynamic and EP evaluation should be performed in the young patient with symptomatic, sustained VT. *(Level of Evidence: C)*

3 ICD therapy in conjunction with pharmacological therapy is indicated for high-risk pediatric patients with a genetic basis (ion channel defects or cardiomyopathy) for either SCD or sustained ventricular arrhythmias. The decision to implant an ICD in a child must consider the risk of SCD associated with the disease, the potential equivalent benefit of medical therapy, as well as risk of device malfunction, infection, or lead failure and that there is reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Class IIa

1 ICD therapy is reasonable for pediatric patients with spontaneous sustained ventricular arrhythmias associated with impaired (LVEF of 35% or less) ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

2 Ablation can be useful in pediatric patients with symptomatic outflow tract or septal VT that is drug resistant, when the patient is drug intolerant or wishes not to take drugs. *(Level of Evidence: C)*

Class III

1 Pharmacological treatment of isolated PVCs in pediatric patients is not recommended. *(Level of Evidence: C)*

2 Digoxin or verapamil should not be used for treatment of sustained tachycardia in infants when VT has not been excluded as a potential diagnosis. *(Level of Evidence: C)*

3 Ablation is not indicated in young patients with asymptomatic NSVT and normal ventricular function. *(Level of Evidence: C)*

Patients with implantable cardioverter–defibrillators

Recommendations

Class I

1 Patients with implanted ICDs should receive regular follow-up and analysis of the device status. *(Level of Evidence: C)*

2 Implanted ICDs should be programmed to obtain optimal sensitivity and specificity. *(Level of Evidence: C)*

3 Measures should be undertaken to minimize the risk of inappropriate ICD therapies. *(Level of Evidence: C)*

4 Patients with implanted ICDs who present with incessant VT should be hospitalized for management. *(Level of Evidence: C)*

Class IIa

1 Catheter ablation can be useful for patients with implanted ICDs who experience incessant or frequently recurring VT. *(Level of Evidence: B)*
2 In patients experiencing inappropriate ICD therapy, EP evaluation can be useful for diagnostic and therapeutic purposes. *(Level of Evidence: C)*

Digitalis toxicity

Recommendations

Class I

An anti-digitalis antibody is recommended for patients who present with sustained ventricular arrhythmias, advanced AV block, and/or asystole that are considered due to digitalis toxicity. *(Level of Evidence: A)*

Class IIa

1 Patients taking digitalis who present with mild cardiac toxicity (e.g., isolated ectopic beats only) can be managed effectively with recognition, continuous monitoring of cardiac rhythm, withdrawal of digitalis, restoration of normal electrolyte levels (including serum potassium greater than 4 mM/L), and oxygenation. *(Level of Evidence: C)*
2 Magnesium or pacing is reasonable for patients who take digitalis and present with severe toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole). *(Level of Evidence: C)*

Class IIb

Dialysis for the management of hyperkalemia may be considered for patients who take digitalis and present with severe toxicity (sustained ventricular arrhythmias; advanced AV block, and/or asystole). *(Level of Evidence: C)*

Class III

Management by lidocaine or phenytoin is not recommended for patients taking digitalis and who present with severe toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole). *(Level of Evidence: C)*

Drug-induced long QT syndrome (Table 17.6) [56–58]

Recommendations

Class I

In patients with drug-induced LQTS, removal of the offending agent is indicated. *(Level of Evidence: A)*

Class IIa

1 Management with intravenous magnesium sulfate is reasonable for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in which the QT remains long. *(Level of Evidence: B)*
2 Atrial or ventricular pacing or isoproterenol is reasonable for patients taking QT-prolonging drugs who present with recurrent torsades de pointes. *(Level of Evidence: B)*

Class IIb

Potassium ion repletion to 4.5 to 5 mmol/L may be reasonable for patients who take QT-prolonging

Table 17.6 Examples of drugs causing torsades de pointes

- Frequent (greater than 1%) (e.g., hospitalization for monitoring recommended during drug initiation in some circumstances)
  - Disopyramide
  - Dofetilide
  - Ibutilide
  - Procainamide
  - Quinidine
  - Sotalol
  - Ajmaline
- Less frequent
  - Amiodarone
  - Arsenic trioxide
  - Bepridil
  - Cisapride
  - Anti-infectives: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
  - Anti-emetics: domperidone, droperidol
  - Antipsychotics: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
  - Opioid dependence agents: methadone

See www.torsades.org for up-to-date listing. Adapted with permission from Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22. Copyright & 2004 Massachusetts Medical Society.1025

drugs and present with few episodes of torsades de pointes in whom the QT remains long. *(Level of Evidence: C)*

Sodium channel blocker-related toxicity

Recommendations

Class I

In patients with sodium channel blocker-related toxicity, removal of the offending agent is indicated. *(Level of Evidence: A)*

Class IIa

1 Stopping the drug, reprogramming the pacemaker or repositioning leads can be useful in patients taking sodium channel blockers who present with elevated defibrillation thresholds or pacing requirement. *(Level of Evidence: C)*

2 In patients taking sodium channel blockers who present with atrial flutter with 1:1 AV conduction, withdrawal of the offending agent is reasonable. If the drug needs to be continued, additional A-V nodal blockade with diltiazem, verapamil, or beta-blocker or atrial flutter ablation can be effective. *(Level of Evidence: C)*

Class IIb

Administration of a beta-blocker and a sodium bolus may be considered for patients taking sodium channel blockers if the tachycardia becomes more frequent or more difficult to cardiovert. *(Level of Evidence: C)*

Other drug-induced toxicity

Recommendations

Class I

1 High intermittent doses and cumulative doses exceeding the recommended levels should be avoided in patients receiving anthracyclines such as doxorubicin. *(Level of Evidence: B)*

2 All patients receiving 5-fluorouracil therapy should receive close supervision and immediate discontinuation of the infusion if symptoms or signs of myocardial ischemia occur. Further treatment with 5-fluorouracil must be avoided in these individuals. *(Level of Evidence: C)*

3 Patients with known cardiac disease should have a full cardiac assessment including echocardiography, which should be undertaken prior to use of anthracyclines such as doxorubicin, and regular long-term follow-up should be considered. *(Level of Evidence: C)*

Ongoing trials and future directions

There remain a significant number of unexplained sudden cardiac deaths. Registries continue to collect information and tissue samples relating to these deaths, hoping to identify biomarkers or genetic clues. There are several ongoing trials exploring the value of new and simpler techniques of resuscitation. The value of automatic external defibrillators is being actively assessed in a variety of community settings.

Sudden cardiac death continues to occur in patients without previous cardiac disease. Risk factors for the prediction of sudden cardiac death and for ICD indication are imperfect, relying for the most part on estimates of left ventricular function. A number of large scale trials and many small studies search for better risk factors in a wide variety of disease states, for example post MI, dilated cardiomyopathy, hypertrophic cardiomyopathy, Brugada syndrome, end-stage renal disease, diabetes, athletes, muscular dystrophy, etc.

The risk predictors of T wave alternans, heart rate variability such as heart rate deceleration capacity and turbulence are being intensively investigated. Recently, the results with microvolt T wave alternans have been disappointing. The ABCD clinical study, which was designed to determine if a T-Wave Alternans (TWA) test is equivalent to an Electrophysiology Study (EPS), reported that both tests were only modestly valuable but the combination was superior. The MASTER II (Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients) failed to identify post-MI patients at higher risk of sudden cardiac death.

There are several ongoing studies of novel antiarrhythmic and other therapies (for example hormone replacement, omega 3 fatty acids, statins, angiotensin receptor blocking agents) for the reduction of sudden death and ventricular arrhythmias in large post MI or heart failure populations and in specific situations such as the long QT syndrome.

There is a surprising number of small trials of ICD therapy for primary prevention of sudden cardiac death in miscellaneous populations. One large ongoing study is the MADIT-CRT trial which

seeks to determine whether combined implantable cardiac defibrillator (ICD)-cardiac resynchronization therapy (CRT-D) will reduce the risk of mortality and heart failure (HF) events in patients with nonischemic or ischemic cardiomyopathy.

There are several early studies of the value of stem cell therapy for the reduction of ventricular arrhythmias, particularly after myocardial infarction. To date conflicting result have been reported.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book these relevant AHA statements and guidelines were published: Reducing Barriers for Implementation of Bystander-Initiated Cardiopulmonary Resuscitation, http://circ.ahajournals.org/cgi/content/full/117/5/704; Essential Features of Designating Out-of-Hospital Cardiac Arrest as a Reportable Event, http://circ.ahajournals.org/cgi/content/full/117/17/2299; Hands-Only (Compression-Only) Cardiopulmonary Resuscitation: A Call to Action for Bystander Response to Adults Who Experience Out-of-Hospital Sudden Cardiac Arrest, http://circ.ahajournals.org/cgi/content/full/117/16/2162; ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, http://circ.ahajournals.org/cgi/content/full/117/21/e350; Sleep Apnea and Cardiovascular Disease, http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.189420.

18 Valvular Heart Disease

Robert O. Bonow

Introduction
Echocardiography
Quantification of severity of valve disease
Endocarditis prophylaxis
Rheumatic fever prophylaxis
Specific valve lesions
Aortic stenosis
Echocardiography (imaging, spectral, and color Doppler) in AS
Exercise testing
Indications for cardiac catheterization
Low-flow/low-gradient AS
Indications for aortic valve replacement
Aortic balloon valvotomy
Aortic regurgitation
Diagnosis and initial evaluation
Medical therapy
Indications for cardiac catheterization
Indications for aortic valve replacement or repair
Bicuspid aortic valve with dilated ascending aorta
Management
Mitral stenosis
Indications for echocardiography
Medical therapy: prevention of systemic embolization
Indications for invasive hemodynamic evaluation
Indications for percutaneous mitral balloon valvotomy
Indications for surgery
Mitral valve prolapse
Evaluation of the asymptomatic patient
Evaluation and management of the symptomatic patient
Mitral regurgitation
Indications for transthoracic echocardiography
Indications for transesophageal echocardiography
Indications for cardiac catheterization
Indications for surgery
Ischemic mitral regurgitation
Tricuspid valve disease
Management
Endocarditis
Indications for transthoracic echocardiography
Indications for transesophageal echocardiography
Surgery for native valve endocarditis
Surgery for prosthetic valve endocarditis
Selection of valve prostheses
Selection of an aortic valve prosthesis
Selection of a mitral valve prosthesis
Future directions

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Introduction

During the past two decades, major advances have occurred in diagnostic techniques, the understanding of natural history, and interventional cardiology and surgical procedures for patients with valvular heart disease. These advances have resulted in enhanced diagnosis, more scientific selection of patients for surgery or catheter-based intervention versus medical management, and increased survival of patients with these disorders. The information base from which to make clinical management decisions has greatly expanded in recent years, yet in many situations, management issues remain controversial or uncertain. Unlike many other forms of cardiovascular disease, there is a scarcity of large-scale multicenter trials addressing the diagnosis and treatment of patients with valvular disease from which to derive definitive conclusions, and the information available in the literature represents primarily the experiences reported by single institutions in relatively small numbers of patients.

The 1998 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease compiled this information base and made recommendations for diagnostic testing, treatment, and physical activity [1]. These guidelines were extensively revised in 2006 [2], and the major recommendations of the 2006 guidelines are discussed in this chapter.

The European Society of Cardiology guidelines for the management of valvular heart disease (3) were published in 2007 and are remarkably concordant with the ACC/AHA recommendations. Where applicable, the ESC recommendations are noted in context with the ACC/AHA recommendations which follow. **The ESC recommendations are primarily focused on indications for surgery and percutaneous intervention, and these are highlighted in Purple.**

Echocardiography

Class I

1 Echocardiography is recommended for asymptomatic patients with diastolic murmurs, continuous murmurs, holosystolic murmurs, late systolic murmurs, or murmurs associated with ejection clicks or that radiate to the neck or back. *(Level of Evidence: C)*

2 Echocardiography is recommended for patients with heart murmurs and symptoms or signs of heart failure, myocardial ischemia/infarction, syncope, thromboembolism, infective endocarditis, or other clinical evidence of structural heart disease. *(Level of Evidence: C)*

3 Echocardiography is recommended for asymptomatic patients who have grade 3 or louder midpeaking systolic murmurs. *(Level of Evidence: C)*

Class IIa

1 Echocardiography can be useful for the evaluation of asymptomatic patients with murmurs associated with other abnormal cardiac physical findings or murmurs associated with an abnormal ECG or chest X-ray. *(Level of Evidence: C)*

2 Echocardiography can be useful for patients whose symptoms and/or signs are likely noncardiac in origin but in whom a cardiac basis cannot be excluded by standard evaluation. *(Level of Evidence: C)*

Class III

1 Echocardiography is not recommended for patients who have a grade 2 or softer midsystolic murmur identified as innocent or functional by an experienced observer. *(Level of Evidence: C)*

Quantification of severity of valve disease

Classification of the severity of valve disease in adults is listed in Table 18.1. The classification for regurgitant lesions is adapted from the recommendations of the American Society of Echocardiography. Subsequent sections of the current guidelines refer to the criteria in Table 18.1 to define severe valvular stenosis or regurgitation. The ESC guidelines use the same classification system for severe aortic stenosis, aortic regurgitation, and mitral regurgitation [3].

Endocarditis prophylaxis

The following information is based on updated recommendations made by the AHA in 2007 [4] and the 2008 focused update of the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease [5].

Class IIa

Prophylaxis against infective endocarditis is probably recommended for the following high risk patients for dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa:

- Prosthetic cardiac valve or prosthetic material used in cardiac valve repair *(Level of Evidence: C)*
- Previous IE *(Level of Evidence: C)*
- Congenital heart disease (CHD) including:
  - Unrepaired cyanotic CHD, including palliative shunts and conduits. *(Level of Evidence: C)*
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. *(Level of Evidence: C)*
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization). *(Level of Evidence: C)*
- Cardiac transplant recipients who develop cardiac valvulopathy *(Level of Evidence: C)*

Table 18.1. Classification of the severity of valve disease in adults

Aortic stenosis			
	Mild	**Moderate**	**Severe**
Jet velocity (m per second)	Less than 3.0	3.0–4.0	Greater than 4.0
Mean gradient (mm Hg)*	Less than 25	25–40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
Valve area index (cm^2/m^2)			Less than 0.6
Mitral stenosis			
	Mild	**Moderate**	**Severe**
Mean gradient (mm Hg)*	Less than 5	5–10	Greater than 10
Pulmonary artery systolic pressure (mmHg)	Less than 30	30–50	Greater than 50
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
Aortic regurgitation**			
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width Greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.6	Greater than 0.6
Quantitative (cath or echo)			
Regurgitant volume (ml/beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.10	0.10–0.29	Greater than or equal to 0.30
Additional Essential Criteria			
Left ventricular size			Increased
Mitral regurgitation**			
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (less than 4 cm^2 or less than 20% LA area)	Signs of MR greater than mild present, but no criteria for severe MR	Vena contracta width greater than 0.7 cm with large central MR jet (area greater than 40% of LA area) or with a wall-impinging jet of any size, swirling in LA
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.69	Greater than or equal to 0.70

Table 18.1. *Continued*

Mitral regurgitation**			
	Mild	**Moderate**	**Severe**
Quantitative (cath or echo)			
Regurgitant volume (ml/beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.20	0.2–0.39	Greater than or equal to 0.40
Additional essential criteria			
Left atrial size			Enlarged
Left ventricular size			Enlarged

Right-sided valve disease	
Severe tricuspid stenosis	Valve area less than 1.0 cm^2
Severe tricuspid regurgitation	Vena contracta width greater than 0.7 cm and systolic flow reversal in hepatic veins
Severe pulmonic stenosis	Jet velocity greater than 4 m per second or maximum gradient greater than 60 mm Hg
Severe pulmonic regurgitation	Color jet fills outflow tract
	Dense continuous wave Doppler signal with a steep deceleration slope

* Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve.

** Quantitation of valvular regurgitation adopted from Zoghbi WA, Enriquez-Sarano M, Foster E, *et al.* Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

The ESC guidelines provide identical definitions of severe aortic stenosis, aortic regurgitation, and mitral regurgitation [3].

Rheumatic fever prophylaxis

Class I

Patients who have had rheumatic fever with or without carditis (including patients with MS) should receive prophylaxis for recurrent rheumatic fever. *(Level of Evidence: B)*

Specific valve lesions

Aortic stenosis

Echocardiography (imaging, spectral, and color Doppler) in AS

Class I

1 Echocardiography is recommended for the diagnosis and assessment of AS severity. *(Level of Evidence: B)*

2 Echocardiography is recommended in patients with AS for the assessment of LV wall thickness, size, and function. *(Level of Evidence: B)*

3 Echocardiography is recommended for re-evaluation of patients with known AS and changing symptoms or signs. *(Level of Evidence: B)*

4 Echocardiography is recommended for the assessment of changes in hemodynamic severity and LV function in patients with known AS during pregnancy. *(Level of Evidence: B)*

5 Transthoracic echocardiography is recommended for re-evaluation of asymptomatic patients: every year for severe AS; every 1 to 2 years for moderate AS; and every 3 to 5 years for mild AS. *(Level of Evidence: B)*

Exercise testing

Class IIb

Exercise testing in asymptomatic patients with AS may be considered to elicit exercise induced symptoms and abnormal blood pressure responses. *(Level of Evidence: B)*

Class III

Exercise testing should not be performed in symptomatic patients with AS. *(Level of Evidence: B)*

Indications for cardiac catheterization

Class I

1 Coronary angiography is recommended before AVR in patients with AS at risk for CAD. *(Level of Evidence: B)* ESC recommendation, class I (C)

2 Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of AS in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS. *(Level of Evidence: C)*

3 Coronary angiography is recommended before AVR in patients with AS for whom a pulmonary autograft (Ross procedure) is contemplated and if the origin of the coronary arteries was not identified by noninvasive technique. *(Level of Evidence: C)*

Class III

1 Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of severity of AS before AVR when noninvasive tests are adequate and concordant with clinical findings. *(Level of Evidence: C)*

2 Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of LV function and severity of AS in asymptomatic patients. *(Level of Evidence: C)*

Low-flow/low-gradient AS

Class IIa

1 Dobutamine stress echocardiography is reasonable to evaluate patients with low-gradient AS and LV dysfunction. *(Level of Evidence: B)*

2 Cardiac catheterization for hemodynamic measurements with infusion of dobutamine can be useful for evaluation of patients with low-flow/low-gradient AS and LV dysfunction. *(Level of Evidence: C)*

Indications for aortic valve replacement (Fig 18.1)

Class I

1 Aortic valve replacement is indicated for symptomatic patients with severe AS.* *(Level of Evidence: B)* ESC recommendation, I (B)

2 Aortic valve replacement is indicated for patients with severe AS* undergoing coronary artery bypass graft surgery (CABG). *(Level of Evidence: C)* ESC recommendation, I (C)

3 Aortic valve replacement is indicated for patients with severe AS* undergoing surgery on the aorta or other heart valves. *(Level of Evidence: C)* ESC recommendation, I (C)

4 Aortic valve replacement is recommended for patients with severe AS* and LV systolic dysfunction (ejection fraction less than 0.50). *(Level of Evidence: C)* ESC recommendation, I (C)

Class IIa

Aortic valve replacement is reasonable for patients with moderate AS* undergoing CABG or surgery on the aorta or other heart valves. *(Level of Evidence: B)* ESC recommendation, IIa (C)

Class IIb

1 Aortic valve replacement may be considered for asymptomatic patients with severe AS* and abnormal response to exercise (e.g., asymptomatic hypotension). *(Level of Evidence: C)* ESC recommendation, I (C) for exercise-induced symptoms, IIa (C) for asymptomatic hypotension, IIb (C) for exercise-induced complex ventricular arrhythmias. Note: exercise-induced symptoms not listed separately in ACC/AHA guidelines as this is considered symptomatic AS [class I (B) above].

2 Aortic valve replacement may be considered for adults with severe asymptomatic AS* if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset. *(Level of Evidence: C)* ESC recommendation, IIa (C) for asymptomatic AS, moderate-to-severe calcification and rate of peak velocity progression >0.3 m/s per year

3 Aortic valve replacement may be considered in patients undergoing CABG who have mild AS* when there is evidence, such as moderate to severe valve calcification, that progression may be rapid. *(Level of Evidence: C)* No ESC recommendation

4 Aortic valve replacement may be considered for asymptomatic patients with extremely severe AS

* See Table 18.1.

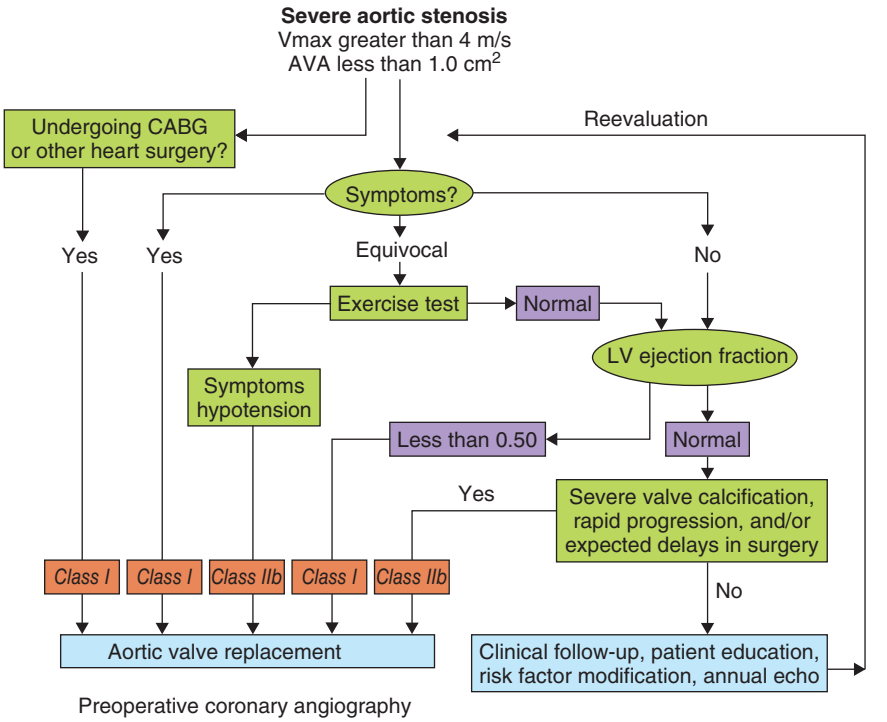

Fig. 18.1 Management strategy for patients with severe aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography.
AVA, aortic valve area; BP, blood pressure; CABG, coronary artery bypass graft surgery; LV, left ventricular; Vmax, maximal velocity across aortic valve by Doppler echocardiography.

(aortic valve area less than 0.6 cm^2, mean gradient greater than 60 mm Hg, and jet velocity greater than 5.0 m per second) when the patient's expected operative mortality is 1.0% or less. *(Level of Evidence: C)*
No ESC recommendation
5 ESC recommendation: AVR for severe AS with excessive hypertrophy (≥15 mm), IIb (C)
6 ESC recommendation: AVR for AS with low gradient (<40 mmHg) and LV dysfunction:
with contractile reserve, IIa (C)
without contractile reserve, IIb (C).

Class III

Aortic valve replacement is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIa/IIb recommendations. *(Level of Evidence: B)*

Aortic balloon valvotomy

Class IIb

1 Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR. *(Level of Evidence: C)* ESC recommendation, IIb (C)
2 Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions. *(Level of Evidence: C)* No ESC recommendation
3 ESC recommendation: Aortic balloon valvotomy for patients with symptomatic severe AS who require urgent major noncardiac surgery, IIb (C)

Class III

Aortic balloon valvotomy is not recommended as an alternative to AVR in adult patients with AS; certain

younger adults without valve calcification may be an exception (see Section 6.1.3). *(Level of Evidence: B)*

Aortic regurgitation

Diagnosis and initial evaluation

Class I

1 Echocardiography is indicated to confirm the presence and severity of acute or chronic AR. *(Level of Evidence: B)*

2 Echocardiography is indicated for diagnosis and assessment of the origin of chronic AR (including valve morphology and aortic root size and morphology) and for assessment of LV hypertrophy, dimension (or volume), and systolic function. *(Level of Evidence: B)*

3 Echocardiography is indicated in patients with an enlarged aortic root to assess regurgitation and the severity of aortic dilatation. *(Level of Evidence: B)*

4 Echocardiography is indicated for the periodic re-evaluation of LV size and function in asymptomatic patients with severe AR. *(Level of Evidence: B)*

5 Radionuclide angiography or magnetic resonance imaging is indicated for the initial and serial assessment of LV volume and function at rest in patients with AR and suboptimal echocardiograms. *(Level of Evidence: B)*

6 Echocardiography is indicated to re-evaluate mild, moderate, or severe AR in patients with new or changing symptoms. *(Level of Evidence: B)*

Class IIa

1 Exercise stress testing for chronic AR is reasonable for assessment of functional capacity and symptomatic response in patients with a history of equivocal symptoms. *(Level of Evidence: B)*

2 Exercise stress testing for patients with chronic AR is reasonable for the evaluation of symptoms and functional capacity before participation in athletic activities. *(Level of Evidence: C)*

3 Magnetic resonance imaging is reasonable for the estimation of AR severity in patients with unsatisfactory echocardiograms. *(Level of Evidence: B)*

Class IIb

Exercise stress testing in patients with radionuclide angiography may be considered for assessment of LV function in asymptomatic or symptomatic patients with chronic AR. *(Level of Evidence: B)*

Medical therapy

Class I

Vasodilator therapy is indicated for chronic therapy in patients with severe AR who have symptoms or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors. *(Level of Evidence: B)*

Class IIa

Vasodilator therapy is reasonable for short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction before proceeding with AVR. *(Level of Evidence: C)*

Class IIb

Vasodilator therapy may be considered for long-term therapy in asymptomatic patients with severe AR who have LV dilatation but normal systolic function. *(Level of Evidence: B)*

Class III

1 Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with mild to moderate AR and normal LV systolic function. *(Level of Evidence: B)*

2 Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for AVR. *(Level of Evidence: C)*

3 Vasodilator therapy is not indicated for long-term therapy in symptomatic patients with either normal LV function or mild to moderate LV systolic dysfunction who are otherwise candidates for AVR. *(Level of Evidence: C)*

Indications for cardiac catheterization

Class I

1 Cardiac catheterization with aortic root angiography and measurement of LV pressure is indicated for assessment of severity of regurgitation, LV function, or aortic root size when noninvasive tests are inconclusive or discordant with clinical findings in patients with AR. *(Level of Evidence: B)*

2 Coronary angiography is indicated before AVR in patients at risk for CAD. *(Level of Evidence: C)*

Class III

1 Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function, aortic root size, or severity of regurgitation before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed. *(Level of Evidence: C)*

2 Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function and severity of regurgitation in asymptomatic patients when noninvasive tests are adequate. *(Level of Evidence: C)*

Indications for aortic valve replacement or repair (Fig. 18.2)

Class I

1 Aortic valve replacement is indicated for symptomatic patients with severe AR irrespective of LV systolic function. *(Level of Evidence: B)* ESC recommendation, I (B)

2 Aortic valve replacement is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfunction (ejection fraction 0.50 or less) at rest. *(Level of Evidence: B)* ESC recommendation, I (B)

3 Aortic valve replacement is indicated for patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves. *(Level of Evidence: C)* ESC recommendation, I (C)

Class IIa

Aortic valve replacement is reasonable for asymptomatic patients with severe AR with normal LV systolic function (ejection fraction greater than 0.50) but with severe LV dilatation (end-diastolic dimension greater than 75 mm or end-systolic dimension greater than 55 mm).* *(Level of Evidence: B)* ESC recommendation, IIa (C) for end-diastolic dimension >70 mm or end-systolic dimension >50 mm (or >25 mm/m^2)

Class IIb

1 Aortic valve replacement may be considered in patients with moderate AR while undergoing surgery on the ascending aorta. *(Level of Evidence: C)* No ESC recommendation

2 Aortic valve replacement may be considered in patients with moderate AR while undergoing CABG. *(Level of Evidence: C)* No ESC recommendation

3 Aortic valve replacement may be considered for asymptomatic patients with severe AR and normal LV systolic function at rest (ejection fraction greater than 0.50) when the degree of LV dilatation exceeds an end-diastolic dimension of 70 mm or end-systolic dimension of 50 mm, when there is evidence of progressive LV dilation, declining exercise tolerance, or abnormal hemodynamic responses to exercise.* *(Level of Evidence: C)* Note: This level of LV dilatation is the ESC recommendation IIa noted above without references to progressive LV dilation, declining exercise tolerance, or abnormal hemodynamic responses to exercise.

Class III

Aortic valve replacement is not indicated for asymptomatic patients with mild, moderate, or severe AR and normal LV systolic function at rest (ejection fraction greater than 0.50) when degree of dilatation is not moderate or severe (end-diastolic dimension less than 70 mm, end-systolic dimension less than 50 mm).* *(Level of Evidence: B)*

Bicuspid aortic valve with dilated ascending aorta

Management

Class I

1 Patients with known bicuspid aortic valves should undergo an initial transthoracic echocardiogram to assess diameter of the aortic root and ascending aorta. *(Level of Evidence: B)*

2 Cardiac magnetic resonance imaging or cardiac computed tomography is indicated in patients with bicuspid aortic valves when morphology of the aortic root or ascending aorta cannot be assessed accurately by echocardiography. *(Level of Evidence: C)*

3 Patients with bicuspid aortic valves and dilatation of the aortic root or ascending aorta (diameter greater than 4.0 cm*) should undergo serial evaluation of aortic root/ascending aorta size and morphology by echocardiography, cardiac magnetic resonance, or computed tomography on a yearly basis. *(Level of Evidence: C)*

* Consider lower threshold values for patients of small stature of either gender.

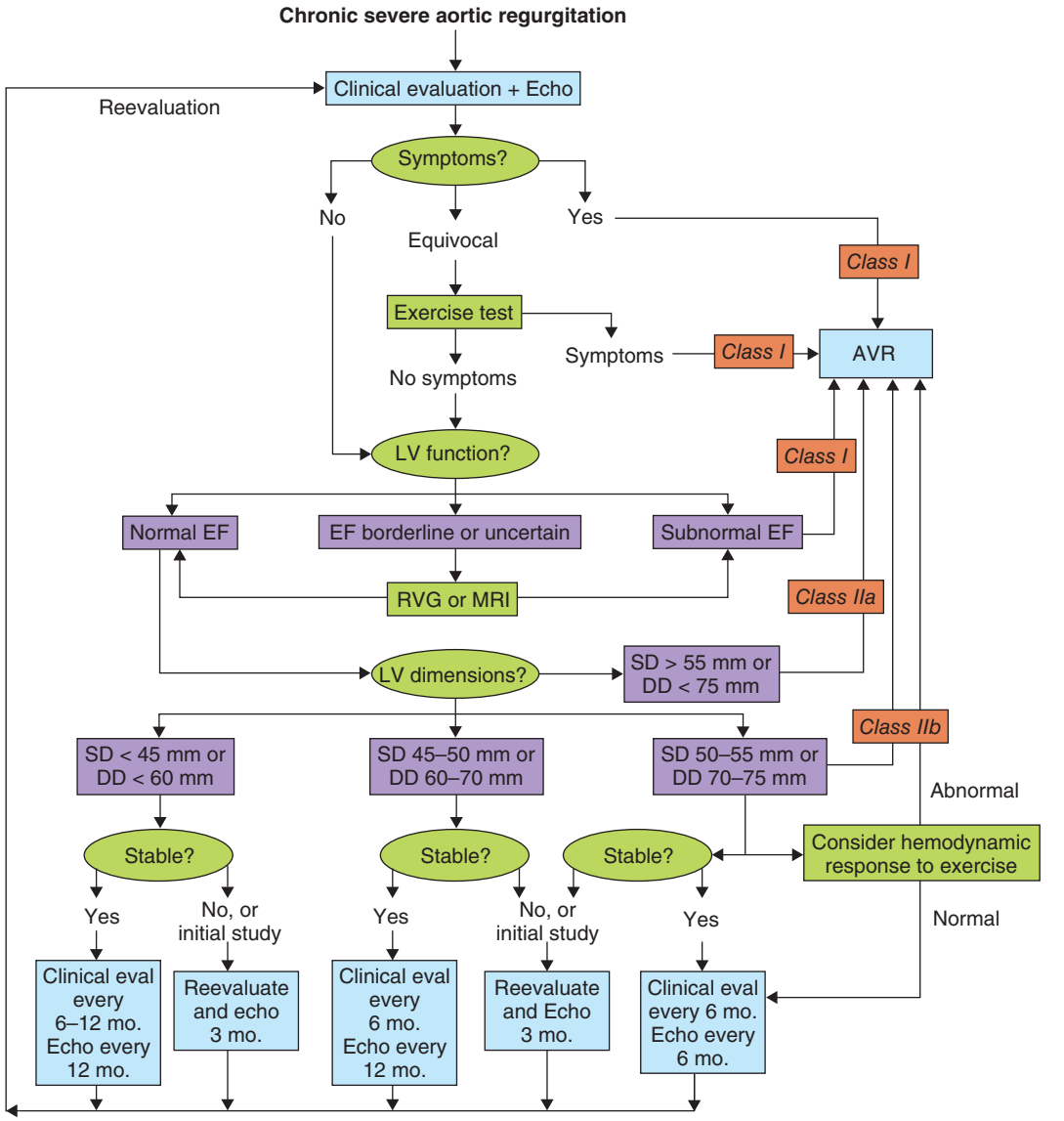

Fig. 18.2 Management strategy for patients with chronic severe aortic regurgitation. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. "Stable" refers to stable echocardiographic measurements. In some centers, serial follow-up may be performed with RVG or MRI rather than echocardiography to assess LV volume and systolic function.
AVR, aortic valve replacement; DD, end-diastolic dimension; EF, ejection fraction; RVG, radionuclide ventriculography; MRI, magnetic resonance imaging; SD, end-systolic dimension.

4 Surgery to repair the aortic root or replace the ascending aorta is indicated in patients with bicuspid aortic valves if the diameter of the aortic root or ascending aorta is greater than 5.0 cm* or if the rate of increase in diameter is 0.5 cm per year or more. *(Level of Evidence: C)* ESC recommendation, IIa (C) for bicuspid valve with diameter of the aortic root or ascending aorta ≥5.0 cm. Recommendations also given for Marfan syndrome with aortic diameter ≥4.5 cm [I (C)] and for all other patients tricuspid aortic valve with aortic diameter ≥5.5 cm [IIa (C)]

5 In patients with bicuspid valves undergoing AVR because of severe AS or AR (see above), repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm.* *(Level of Evidence: C)* No ESC recommendation

Class IIa

1 It is reasonable to give beta-adrenergic blocking agents to patients with bicuspid valves and dilated aortic roots (diameter greater than 4.0 cm*) who are not candidates for surgical correction and who do not have moderate to severe AR. *(Level of Evidence: C)*

2 Cardiac magnetic resonance imaging or cardiac computed tomography is indicated in patients with bicuspid aortic valves when aortic root dilatation is detected by echocardiography to further quantify severity of dilatation and involvement of the ascending aorta. *(Level of Evidence: B)*

Mitral stenosis

Indications for echocardiography

Class I

1 Echocardiography should be performed in patients for the diagnosis of MS, assessment of hemodynamic severity (mean gradient, MV area, and pulmonary artery pressure), assessment of concomitant valvular lesions, and assessment of valve morphology (to determine suitability for percutaneous mitral balloon valvotomy). *(Level of Evidence: B)*

2 Echocardiography should be performed for re-evaluation in patients with known MS and changing symptoms or signs. *(Level of Evidence: B)*

3 Echocardiography should be performed for assessment of the hemodynamic response of the mean gradient and pulmonary artery pressure by exercise Doppler echocardiography in patients with MS when there is a discrepancy between resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. *(Level of Evidence: C)*

4 Transesophageal echocardiography in MS should be performed to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR in patients considered for percutaneous mitral balloon valvotomy. *(Level of Evidence: C)*

5 Transesophageal echocardiography in MS should be performed to evaluate MV morphology and hemodynamics in patients when transthoracic echocardiography provides suboptimal data. *(Level of Evidence: C)*

Class IIa

Echocardiography is reasonable in the re-evaluation of asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure (for those with severe MS, every year; moderate MS, every 1 to 2 years; and mild MS, every 3 to 5 years). *(Level of Evidence: C)*

Class III

Transesophageal echocardiography in the patient with MS is not indicated for routine evaluation of MV morphology and hemodynamics when complete transthoracic echocardiographic data are satisfactory. *(Level of Evidence: C)*

Medical therapy: prevention of systemic embolization

Class I

1 Anticoagulation is indicated in patients with MS and atrial fibrillation (paroxysmal, persistent, or permanent). *(Level of Evidence: B)*

2 Anticoagulation is indicated in patients with MS and a prior embolic event, even in sinus rhythm. *(Level of Evidence: B)*

3 Anticoagulation is indicated in patients with MS with left atrial thrombus. *(Level of Evidence: B)*

Class IIb

1 Anticoagulation may be considered for asymptomatic patients with severe MS and left atrial dimension greater than or equal to 55 mm by echocardiography. *(Level of Evidence: B)*

2 Anticoagulation may be considered for patients with severe MS, an enlarged left atrium, and spontaneous contrast on echocardiography. *(Level of Evidence: C)*

Indications for invasive hemodynamic evaluation

Class I

1 Cardiac catheterization for hemodynamic evaluation should be performed for assessment of severity

* Consider lower threshold values for patients of small stature of either gender.

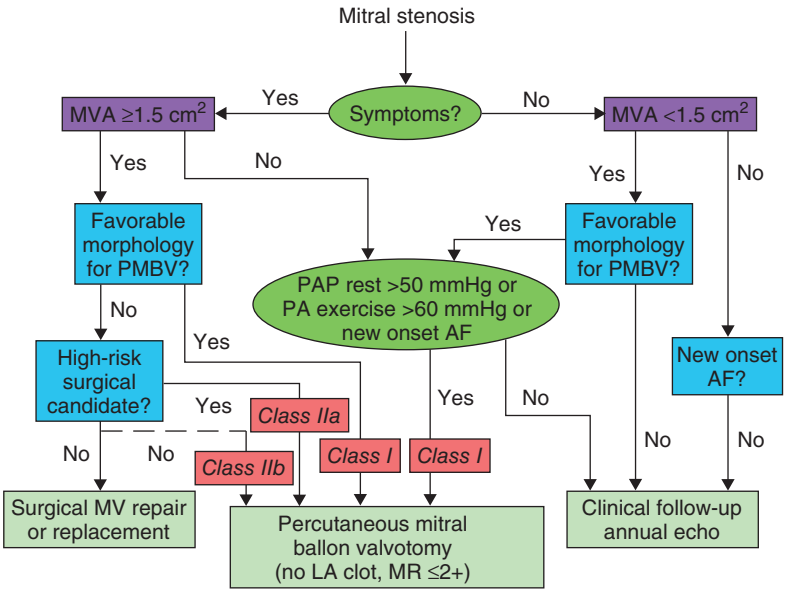

Fig. 18.3 Management strategy for patients with mitral stenosis.
AF, atrial fibrillation; MVA, mitral valve area; PAP, pulmonary artery systolic pressure; PMBV, percutaneous mitral balloon valvotomy. Adapted from Otto CM, Bonow RO. Valvular heart disease. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th edn. Philadelphia: Elsevier Science, 2007:1625–1693.

of MS when noninvasive tests are inconclusive or when there is discrepancy between noninvasive tests and clinical findings regarding severity of MS. *(Level of Evidence: C)*

2 Catheterization for hemodynamic evaluation including left ventriculography (to evaluate severity of MR) for patients with MS is indicated when there is a discrepancy between the Doppler-derived mean gradient and valve area. *(Level of Evidence: C)*

Class IIa

1 Cardiac catheterization is reasonable to assess the hemodynamic response of pulmonary artery and left atrial pressures to exercise when clinical symptoms and resting hemodynamics are discordant. *(Level of Evidence: C)*

2 Cardiac catheterization is reasonable in patients with MS to assess the cause of severe pulmonary arterial hypertension when out of proportion to severity of MS as determined by noninvasive testing. *(Level of Evidence: C)*

Class III

Diagnostic cardiac catheterization is not recommended to assess the MV hemodynamics when 2D and Doppler echocardiographic data are concordant with clinical findings. *(Level of Evidence: C)*

Indications for percutaneous mitral balloon valvotomy (Fig. 18.3)

Class I

1 Percutaneous mitral balloon valvotomy is effective for symptomatic patients (NYHA functional class II, III, or IV), with moderate or severe MS* and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR. (*Level of Evidence: A)* ESC recommendation, I (B)

2 Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe MS* and valve morphology which is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR. *(Level of*

* See Table 18.1.

Evidence: C) ESC recommendation, IIa (C) based on resting measurement >50 mm Hg only

Class IIa

Percutaneous mitral balloon valvotomy is reasonable for patients with moderate or severe MS* who have a nonpliable calcified valve, are in NYHA functional class III-IV, and are either not candidates for surgery or are at high risk for surgery. *(Level of Evidence: C)* ESC recommendation, I (C)

Class IIb

1 Percutaneous mitral balloon valvotomy may be considered for asymptomatic patients with moderate or severe MS* and valve morphology favorable for percutaneous balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: C)* ESC recommendation, IIa (C)

2 Percutaneous mitral balloon valvotomy may be considered for symptomatic patients (NYHA functional class II, III, or IV) with MV area greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery systolic pressure greater than 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient greater than 15 mm Hg during exercise. *(Level of Evidence: C)* No ESC recommendation

3 Percutaneous mitral balloon valvotomy may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA classes III–IV. *(Level of Evidence: C)* ESC recommendation, IIa (C)

4 ESC recommendations: Percutaneous mitral balloon valvotomy for patients with:

- Previous thromboembolism, IIa (C)
- Need for noncardiac surgery, IIa (C)
- Desire for pregnancy, IIa (C)

Class III

1 Percutaneous mitral balloon valvotomy is not indicated for patients with mild MS. *(Level of Evidence: C)*

2 Percutaneous mitral balloon valvotomy should not be performed in patients with moderate to severe MR or left atrial thrombus. *(Level of Evidence: C)*

Indications for surgery (Fig 18.3)

Class I

1 Mitral valve surgery (repair if possible) is indicated in patients with symptomatic (NYHA functional classes III–IV) moderate or severe MS* when (1) percutaneous mitral balloon valvotomy is unavailable; (2) percutaneous mitral balloon valvotomy is contraindicated because of left atrial thrombus despite anticoagulation or because concomitant moderate to severe MR is present; or (3) the valve morphology is not favorable for percutaneous mitral balloon valvotomy in a patient with acceptable operative risk. *(Level of Evidence: B)*

2 Symptomatic patients with moderate to severe MS* who also have moderate to severe MR should receive MV replacement, unless valve repair is possible at the time of surgery. *(Level of Evidence: C)*

Class IIa

Mitral valve replacement is reasonable for patients with severe MS* and severe pulmonary hypertension (pulmonary artery systolic pressure greater than 60 to 80 mm Hg) with NYHA functional class I–II symptoms who are not considered candidates for percutaneous balloon valvotomy or surgical MV repair. *(Level of Evidence: C)*

Class IIb

Mitral valve repair may be considered for asymptomatic patients with moderate or severe MS* who have had recurrent embolic events while receiving adequate anticoagulation and who have valve morphology favorable for repair. *(Level of Evidence: C)*

Class III

1 Mitral valve repair for MS is not indicated for patients with mild MS. *(Level of Evidence: C)*

2 Closed commissurotomy should not be performed in patients undergoing MV repair; open commissurotomy is the preferred approach. *(Level of Evidence: C)*

Mitral valve prolapse

Evaluation of the asymptomatic patient

Class I

Echocardiography should be used for the diagnosis and assessment of hemodynamic severity, leaflet morphology, and ventricular compensation in asymptomatic patients with physical signs of MVP. *(Level of Evidence: B)*

Class IIa

1 Echocardiography can effectively exclude MVP in asymptomatic patients who have been diagnosed

without clinical evidence to support the diagnosis. *(Level of Evidence: C)*

2 Echocardiography can be effective for risk stratification in asymptomatic patients with physical signs of MVP or known MVP. *(Level of Evidence: C)*

Class III

1 Echocardiography is not indicated to exclude MVP in asymptomatic patients with ill-defined symptoms in the absence of a constellation of clinical symptoms or physical findings suggestive of MVP or a positive family history. *(Level of Evidence: B)*

2 Routine repetition of echocardiography is not indicated for the asymptomatic patient who has MVP and no MR or MVP and mild MR with no changes in clinical signs or symptoms. *(Level of Evidence: C)*

Evaluation and management of the symptomatic patient

Class I

1 Aspirin therapy (75 to 325 mg per day) is recommended for symptomatic patients with MVP who experience cerebral transient ischemic attacks. *(Level of Evidence: C)*

2 Warfarin therapy is recommended for patients with MVP and atrial fibrillation who have hypertension, MR murmur, or a history of heart failure or are age 65 years or older *(Level of Evidence: C)*

3 Aspirin therapy (75 to 325 mg per day) is recommended for patients with MVP and atrial fibrillation who are less than 65 years old and have no history of MR, hypertension, or heart failure. *(Level of Evidence: C)*

4 In patients with MVP and a history of stroke, warfarin therapy is recommended for patients with MR, atrial fibrillation, or left atrial thrombus. *(Level of Evidence: C)*

Class IIa

1 In patients with MVP and a history of stroke, who do not have MR, atrial fibrillation, or left atrial thrombus, warfarin therapy is reasonable for patients with echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets. *(Level of Evidence: C)*

2 In patients with MVP and a history of stroke, aspirin therapy is reasonable for patients who do not have MR, atrial fibrillation, left atrial thrombus, or echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets. *(Level of Evidence: C)*

3 Warfarin therapy is reasonable for patients with MVP with transient ischemic attacks despite aspirin therapy. *(Level of Evidence: C)*

4 Aspirin therapy (75 to 325 mg per day) can be beneficial for patients with MVP and a history of stroke who have contraindications to anticoagulants. *(Level of Evidence: B)*

Class IIb

Aspirin therapy (75 to 325 mg per day) may be considered for patients in sinus rhythm with echocardiographic evidence of high-risk MVP. *(Level of Evidence: C)*

Mitral regurgitation

Indications for transthoracic echocardiography

Class I

1 Transthoracic echocardiography is indicated for baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure, and severity of MR (Table 18.1) in any patient suspected of having MR. *(Level of Evidence: C)*

2 Transthoracic echocardiography is indicated for delineation of the mechanism of MR. *(Level of Evidence: B)*

3 Transthoracic echocardiography is indicated for annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate to severe MR. *(Level of Evidence: C)*

4 Transthoracic echocardiography is indicated in patients with MR to evaluate the MV apparatus and LV function after a change in signs or symptoms. *(Level of Evidence: C)*

5 Transthoracic echocardiography is indicated to evaluate LV size and function and MV hemodynamics in the initial evaluation after MV replacement or MV repair. *(Level of Evidence: C)*

Class IIa

Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity. *(Level of Evidence: C)*

Class III
Transthoracic echocardiography is not indicated for routine follow-up evaluation of asymptomatic patients with mild MR and normal LV size and systolic function. *(Level of Evidence: C)*

Indications for transesophageal echocardiography

Class I
1 Preoperative or intraoperative transesophageal echocardiography is indicated to establish the anatomic basis for severe MR in patients in whom surgery is recommended to assess feasibility of repair and to guide repair. *(Level of Evidence: B)*

2 Transesophageal echocardiography is indicated for evaluation of MR patients in whom transthoracic echocardiography provides nondiagnostic information regarding severity of MR, mechanism of MR, and/or status of LV function. *(Level of Evidence: B)*

Class IIa
Preoperative transesophageal echocardiography is reasonable in asymptomatic patients with severe MR who are considered for surgery to assess feasibility of repair. *(Level of Evidence: C)*

Class III
Transesophageal echocardiography is not indicated for routine follow-up or surveillance of asymptomatic patients with native valve MR. *(Level of Evidence: C)*

Indications for cardiac catheterization

Class I
1 Left ventriculography and hemodynamic measurements are indicated when noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery. *(Level of Evidence: C)*

2 Hemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR as assessed by noninvasive testing. *(Level of Evidence: C)*

3 Left ventriculography and hemodynamic measurements are indicated when there is a discrepancy between clinical and noninvasive findings regarding severity of MR. *(Level of Evidence: C)*

4 Coronary angiography is indicated before MV repair or MV replacement in patients at risk for CAD. *(Level of Evidence: C)*

Class III
Left ventriculography and hemodynamic measurements are not indicated in patients with MR in whom valve surgery is not contemplated. *(Level of Evidence: C)*

Indications for surgery (Fig 18.4)

Class I
1 Mitral valve surgery is recommended for the symptomatic patient with acute severe MR.* *(Level of Evidence: B)* No ESC recommendation

2 Mitral valve surgery is beneficial for patients with chronic severe MR* and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction less than 0.30) and/or end-systolic dimension greater than 55 mm. *(Level of Evidence: B)* ESC recommendation, I (B)

3 Mitral valve surgery is beneficial for asymptomatic patients with chronic severe MR* and mild to moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end-systolic dimension greater than or equal to 40 mm. *(Level of Evidence: B)* ESC recommendation, I (C) for EF ≤0.60 but note end-systolic dimension threshold of ≥45 mm.

4 Mitral valve repair is recommended over MV replacement in the majority of patients with severe chronic MR* who require surgery, and patients should be referred to surgical centers experienced in MV repair. *(Level of Evidence: C)* No ESC recommendation

Class IIa
1 Mitral valve repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR* with preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom the likelihood of successful repair without residual MR is greater than 90%. *(Level of Evidence: B)* ESC recommendation, IIb (B)

2 Mitral valve surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and new onset of atrial fibrillation. *(Level of Evidence: C)* ESC recommendation, IIa (C) without stipulation for "new" atrial fibrillation

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*Severe MR as defined objectively in Table 18.1.

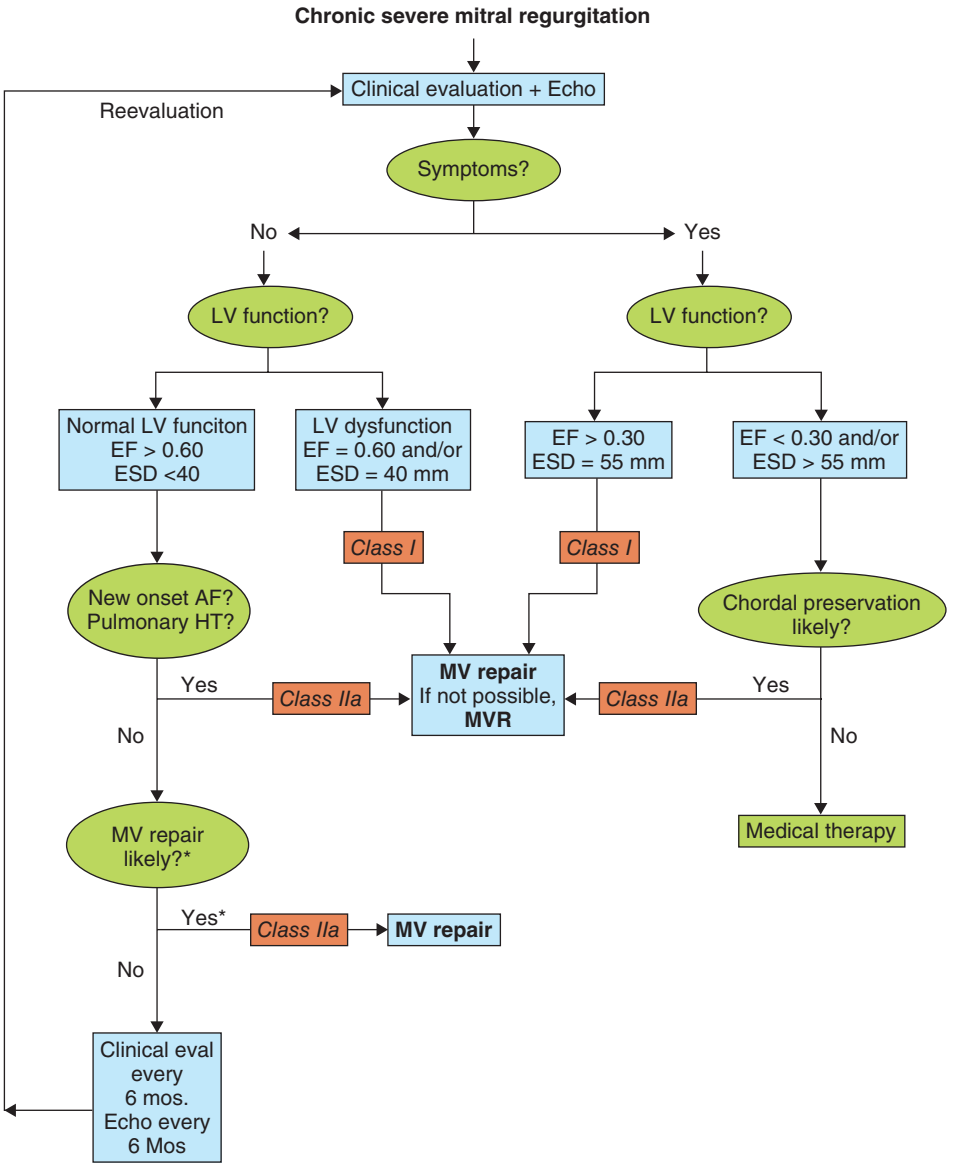

Fig. 18.4 Management strategy for patients with chronic severe mitral regurgitation.
*Mitral valve repair may be performed in asymptomatic patients with normal LV function if performed by an experienced surgical team and the likelihood of successful MV repair is greater than 90%.
AF, atrial fibrillation; EF, ejection fraction; ESD, end-systolic dimension; HT, hypertension; MV, mitral valve; MVR, mitral valve repair.

3 Mitral valve surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise). *(Level of Evidence: C)* ESC recommendation, IIa (C) for resting measurement ≥50 mm Hg only

4 Mitral valve surgery is reasonable for patients with chronic severe MR* due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction

(ejection fraction less than 0.30 and/or end-systolic dimension greater than 55 mm) in whom MV repair is highly likely. *(Level of Evidence: C)* ESC recommendation, IIa (C) for those is whom durable repair is likely but IIb (C) for those in whom successful repair is unlikely

Class IIb

Mitral valve repair may be reasonable for patients with chronic severe secondary MR* due to severe LV dysfunction (ejection fraction less than 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing. *(Level of Evidence: C)* No ESC recommendation

Class III

1 Mitral valve surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom significant doubt about the feasibility of repair exists. *(Level of Evidence: C)*

2 Isolated MV surgery is not indicated for patients with mild or moderate MR. *(Level of Evidence: C)*

Ischemic mitral regurgitation

CABG alone is usually insufficient and leaves many patients with significant residual MR, and these patients would benefit from concomitant MV repair at the time of the CABG. Mitral annuloplasty alone with a downsized annuloplasty ring is often effective at relieving MR. There were no specific ACC/AHA class recommendations, but the ESC guidelines provide the following recommendations:

1 ESC recommendation: Patients with severe MR, LV ejection fraction >0.30 undergoing CABG, class I (C).

2 ESC recommendation: Patients with moderate MR undergoing CABG if repair is feasible, class IIa (C).

3 ESC recommendation: Symptomatic patients with severe MR, LV ejection fraction <0.30 and option for revascularization, class IIa (C).

4 ESC recommendation: Patients with severe MR, LV ejection fraction <0.30, no option for revascularization, refractory to medical therapy, and low comorbidity, class IIb (C).

Tricuspid valve disease

Management

Class I

Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery. *(Level of Evidence: B)* ESC recommendation, I (C) for severe TR in patients undergoing left-sided valve surgery

Class IIa

1 Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic. *(Level of Evidence: C)* ESC recommendation, I (C)

2 Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair. *(Level of Evidence: C)* No ESC recommendation

3 ESC recommendation: Severe TR and symptoms, after left-sided valve surgery, in the absence of left-sided myocardial, valve, or RV dysfunction and without severe pulmonary hypertension (systolic pulmonary artery pressure >60 mm Hg), IIa (C).

Class IIb

1 Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation. *(Level of Evidence: C)* ESC recommendation, IIa (C), with definition of tricuspid annular dilatation of >40 mm

2 ESC recommendation: Severe isolated TR with mild or no symptoms and progressive dilation or deterioration of RV function, IIb (C).

Class III

1 Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mm Hg in the presence of a normal MV. *(Level of Evidence: C)*

2 Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR. *(Level of Evidence: C)*

Endocarditis

Indications for transthoracic echocardiography

Class I

1 Transthoracic echocardiography to detect valvular vegetations with or without positive blood cul-

tures is recommended for the diagnosis of infective endocarditis. *(Level of Evidence: B)*

2 Transthoracic echocardiography is recommended to characterize the hemodynamic severity of valvular lesions in known infective endocarditis. *(Level of Evidence: B)*

3 Transthoracic echocardiography is recommended for assessment of complications of infective endocarditis (e.g., abscesses, perforation, and shunts). *(Level of Evidence: B)*

4 Transthoracic echocardiography is recommended for reassessment of high-risk patients (e.g., those with a virulent organism, clinical deterioration, persistent or recurrent fever, new murmur, or persistent bacteremia). *(Level of Evidence: C)*

Class IIa

Transthoracic echocardiography is reasonable to diagnose infective endocarditis of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur. *(Level of Evidence: C)*

Class IIb

Transthoracic echocardiography may be considered for the re-evaluation of prosthetic valve endocarditis during antibiotic therapy in the absence of clinical deterioration. *(Level of Evidence: C)*

Class III

Transthoracic echocardiography is not indicated to re-evaluate uncomplicated (including no regurgitation on baseline echocardiogram) native valve endocarditis during antibiotic treatment in the absence of clinical deterioration, new physical findings or persistent fever. *(Level of Evidence: C)*

Indications for transesophageal echocardiography

Class I

1 Transesophageal echocardiography is recommended to assess the severity of valvular lesions in symptomatic patients with infective endocarditis, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*

2 Transesophageal echocardiography is recommended to diagnose infective endocarditis in patients with valvular heart disease and positive blood cultures, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*

3 Transesophageal echocardiography is recommended for diagnosing complications of infective endocarditis with potential impact on prognosis and management, for example, abscess, perforation, and shunts. *(Level of Evidence: C)*

4 Transesophageal echocardiography is recommended as first-line diagnostic study to diagnose prosthetic valve endocarditis and assess for complications. *(Level of Evidence: C)*

5 Transesophageal echocardiography is recommended for preoperative evaluation in patients with known infective endocarditis, unless the need for surgery is evident on transthoracic imaging and unless preoperative imaging will delay surgery in urgent cases. *(Level of Evidence: C)*

6 Intraoperative transesophageal echocardiography is recommended for patients undergoing valve surgery for infective endocarditis. *(Level of Evidence: C)*

Class IIa

Transesophageal echocardiography is reasonable to diagnose possible infective endocarditis in patients with persistent staphylococcal bacteremia without a known source. *(Level of Evidence: C)*

Class IIb

Transesophageal echocardiography might be considered to detect infective endocarditis in patients with nosocomial staphylococcal bacteremia. *(Level of Evidence: C)*

Surgery for native valve endocarditis

Class I

1 Surgery of the native valve is indicated in patients with acute infective endocarditis who present with valve stenosis or regurgitation resulting in heart failure. *(Level of Evidence: B)*

2 Surgery of the native valve is indicated in patients with acute infective endocarditis who present with AR or MR with hemodynamic evidence of elevated LV end-diastolic or left atrial pressures (e.g., premature closure of MV with AR, rapid decelerating MR signal by continuous-wave Doppler (*v*-wave cutoff sign), or moderate or severe pulmonary hypertension). *(Level of Evidence: B)*

3 Surgery of the native valve is indicated in patients with infective endocarditis caused by fungal or other highly resistant organisms. *(Level of Evidence: B)*

4 Surgery of the native valve is indicated in patients with infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (e.g., sinus of Valsalva to right atrium, RV, or left atrium fistula; mitral leaflet perforation with aortic valve endocarditis; or infection in annulus fibrosa). *(Level of Evidence: B)*

Class IIa

Surgery of the native valve is reasonable in patients with infective endocarditis who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy. *(Level of Evidence: C)*

Class IIb

Surgery of the native valve may be considered in patients with infective endocarditis who present with mobile vegetations in excess of 10 mm with or without emboli. *(Level of Evidence: C)*

Surgery for prosthetic valve endocarditis

Class I

1 Consultation with a cardiac surgeon is indicated for patients with infective endocarditis of a prosthetic valve. *(Level of Evidence: C)*

2 Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with heart failure. *(Level of Evidence: B)*

3 Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with dehiscence evidenced by cine fluoroscopy or echocardiography. *(Level of Evidence: B)*

4 Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with evidence of increasing obstruction or worsening regurgitation. *(Level of Evidence: C)*

5 Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with complications, for example, abscess formation. *(Level of Evidence: C)*

Class IIa

1 Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with evidence of persistent bacteremia or recurrent emboli despite appropriate antibiotic treatment. *(Level of Evidence: C)*

2 Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with relapsing infection. *(Level of Evidence: C)*

Class III

Routine surgery is not indicated for patients with uncomplicated infective endocarditis of a prosthetic valve caused by first infection with a sensitive organism. *(Level of Evidence: C)*

Selection of valve prostheses

Selection of an aortic valve prosthesis

Class I

1 A mechanical prosthesis is recommended for AVR in patients with a mechanical valve in the mitral or tricuspid position. *(Level of Evidence: C)* ESC recommendation, I (C)

2 A bioprosthesis is recommended for AVR in patients of any age who will not take warfarin or who have major medical contraindications to warfarin therapy. *(Level of Evidence: C)* ESC recommendation, I (C)

Class IIa

1 Patient preference is a reasonable consideration in the selection of aortic valve operation and valve prosthesis. A mechanical prosthesis is reasonable for AVR in patients less than 65 years of age who do not have a contraindication to anticoagulation. A bioprosthesis is reasonable for AVR in patients under 65 years of age who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future. *(Level of Evidence: C)* ESC recommendation: Desire of the informed patient, I (C)

2 A bioprosthesis is reasonable for AVR in patients aged 65 years or older without risk factors for thromboembolism. *(Level of Evidence: C)* ESC recommendation, IIa (C)

3 Aortic valve re-replacement with a homograft is reasonable for patients with active prosthetic valve endocarditis. *(Level of Evidence: C)* No ESC recommendation

4 ESC recommendation: A bioprosthesis is reasonable for reoperation for mechanical valve thrombosis in a patient with proven poor anticoagulant control, I (C)

Class IIb

A bioprosthesis might be considered for AVR in a woman of childbearing age. *(Level of Evidence: C)* ESC recommendation, IIb (C)

Selection of a mitral valve prosthesis

1 Mitral valve repair is recommended when anatomically possible for patients with severe degenerative MR who fulfill clinical indications, and patients should be referred to surgeons who are expert in repair. *(Level of Evidence: B)* No ESC recommendation

2 A bioprostheses is indicated for MV replacement in a patient who will not take warfarin, is incapable of taking warfarin, or has a clear contraindication to warfarin therapy. *(Level of Evidence: C)* ESC recommendation, I (C)

Class IIa

1 A mechanical prosthesis is reasonable for MV replacement in patients less than 65 years of age with long-standing atrial fibrillation. *(Level of Evidence: C)* ESC recommendation, IIa (C)

2 A bioprosthesis is reasonable for MV replacement in patients 65 years of age or older. *(Level of Evidence: C)* ESC recommendation, IIa (C)

3 A bioprosthesis is reasonable for MV replacement in patients under 65 years of age in sinus rhythm who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second MV replacement may be necessary in the future. *(Level of Evidence: C)* ESC recommendation: Desire of the informed patient, I (C)

Future directions

Guidelines in valvular heart disease are limited by an inadequate number of prospective randomized clinical trials, so that the vast majority of recommendations are based on expert consensus alone *(Level of Evidence C)*. There is a major unmet need for the development of clinical trials to determine the efficacy of medical therapy and the indications for and timing of surgical interventions. This is particularly true in the decisions for surgery in asymptomatic patients and in patients with ischemic MR and other forms of functional MR, in which there is considerable equipoise regarding patient management. There is also a need for development of biomarkers in valvular heart disease, which may identify patients with incipient LV dysfunction at an earlier stage than can now be determined by symptoms or echocardiography evidence of declining systolic function and enlarging chamber size. BNP is a good candidate marker, and with further clinical research, this biomarker and others may become the object of future guidelines. Finally, the field of percutaneous aortic valve replacement and mitral valve repair is moving very rapidly, with prospective randomized trials already underway. These exciting developments are much too preliminary at present for guidelines considerations, but undoubtedly future iterations of the valvular heart disease guidelines with include recommendations for patient selection and device selection. These new devices will also spur the development of clinical trials from which a prospectively derived evidence base will emerge, thus addressing the main limitation noted above in the current guidelines in valvular heart disease.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

19 Infective Endocarditis

Larry M. Baddour, Kathryn A. Taubert, Michael H. Gewitz, and Walter R. Wilson

Introduction
Guidelines for the diagnosis, antimicrobial therapy, and management of complications of infective endocarditis
Diagnosis
Echocardiography
Antimicrobial treatment
Complications and their treatment
Surgical therapy
Congestive heart failure
Risk of embolization
Periannular extension of infection
Mycotic aneurysms
Outpatient therapy
Care at completion of treatment
Short-term follow-up
Long-term follow-up
Guidelines for the prevention of infective endocarditis
History of AHA Statements on prevention of IE
Dental procedures and IE
Cardiac conditions and endocarditis
Prophylaxis for dental procedures in patients with cardiac conditions associated with the highest risk of adverse outcome from endocarditis
Regimens for respiratory tract procedures
Recommendations for GI or GU tract procedures
Regimens for procedures on infected skin, skin structure, or musculoskeletal tissue

Introduction

Two sets of guidelines are reviewed in this chapter and address infective endocarditis (IE). One guideline is dedicated to all aspects of endocarditis diagnosis and management and was updated in 2005; the other examines IE prevention and its latest version was published in 2007.

The writing groups for both guidelines were charged with the task of performing an assessment of the evidence and giving a classification of recommendations and a level of evidence (LOE) to each recommendation. The American College of Cardiology (ACC)/American Heart Association (AHA) classification system was used in each document. (See table in the front of the book.)

Guidelines for the diagnosis, antimicrobial therapy, and management of complications of infective endocarditis

This work represents the third iteration of an infective endocarditis "treatment" document developed by the American Heart Association under the auspices of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease of the Young. It updates recommendations for diagnosis, treatment, and management of complications of infective endocarditis. A multidisciplinary committee of experts drafted this document to assist physicians in the evolving care of patients with infective endocarditis in the new millennium.

Diagnosis

The variability in clinical presentation of IE requires a diagnostic strategy that is both sensitive for disease detection and specific for its exclusion across all forms of the disease. In 1994, Durack and colleagues from Duke University Medical Center proposed a diagnostic schema termed *the Duke criteria*, which

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stratified patients with suspected IE into three categories: "definite" cases, identified either clinically or pathologically (IE proved at surgery or autopsy); "possible" cases (not meeting the criteria for definite IE); and "rejected" cases (no pathological evidence of IE at autopsy or surgery, rapid resolution of the clinical syndrome with either no treatment or short-term antibiotic therapy, or a firm alternative diagnosis). Several refinements have been made recently to both the major and minor Duke criteria. These modified Duke criteria are shown in Tables 19.1a and 19.1b.

Because IE is a heterogeneous disease with highly variable clinical presentations, the use of criteria alone will never suffice. Criteria changes that add sensitivity often do so at the expense of specificity and vice versa. The modified Duke criteria are meant to be a clinical guide for diagnosing IE and must not replace clinical judgment. Clinicians may appropriately and wisely decide whether to treat or not treat an individual patient, regardless of whether they meet or fail to meet the criteria for definite or possible IE by the Duke schema.

Echocardiography

Echocardiography is central to the diagnosis and management of patients with IE. Echocardiographic evidence of an oscillating intracardiac mass or vegetation, an annular abscess, prosthetic valve partial dehiscence, and new valvular regurgitation are major criteria in the diagnosis of IE. Echocardiography should be performed in all cases of suspected IE *(Class I, Level of Evidence: A)*. The algorithm shown in Fig. 19.1 gives an approach to the diagnostic use of echocardiography when IE is suspected and helps in the decision of whether to initially perform transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Recommendations for the timing of echocardiography in diagnosis and management of IE are presented in Table 19.2. An initial echo should be obtained within 12 hours of the initial evaluation. TEE is the preferred imaging technique for the diagnosis and management of IE in adults with either high risk for IE or moderate to high clinical suspicion of IE or in patients in whom imaging TTE is difficult. Transesophageal echocardiography is more sensitive than transthoracic echocardiography for detecting vegetations and cardiac abscess. If the initial TTE images are negative and the diagnosis of IE is still being considered, then TEE should be performed as soon as possible (Table 19.2; *Class I, Level of Evidence: A*). Among patients with an initial positive TTE and a high risk for cardiac complications including perivalvular extension of infection, TEE should be obtained as soon as possible *(Class I, Level of Evidence: A)*. Repeating TEE 7 to 10 days after an initial "negative" result is often advisable *(Class I, Level of Evidence: B)* when clinical suspicion of IE persists. In some cases, vegetations may reach detectable size in the interval, or abscess cavities or fistulous tracts may become clear. An interval increase in vegetation size on serial echocardiography despite the administration of appropriate antibiotic therapy has serious implications and has been associated with an increased risk of complications and the need for surgery. Repeat TEE also may be useful when a patient with an initially positive TEE develops worrisome clinical features during antibiotic therapy *(Class I, Level of Evidence: A)*. Unexplained progression of heart failure symptoms, change in cardiac murmurs, and new atrioventricular block or arrhythmia should prompt emergent evaluation by TEE if possible or by TTE if necessary to minimize delay.

Several echocardiographic features identify patients at high risk for a complicated course or with a need for surgery (Table 19.3). These features include large vegetations, severe valvular insufficiency, abscess cavities or pseudoaneurysms, valvular perforation or dehiscence, and evidence of decompensated heart failure. The ability of echocardiographic features to predict embolic events is limited. The greatest risk appears to occur with large vegetations (>10 mm in diameter) on the anterior mitral leaflet. Vegetation size and mobility must be taken into account, along with bacteriologic factors and other indications for surgery, when considering early surgery to avoid embolization.

Antimicrobial treatment

Results of clinical efficacy studies support the use of most treatment regimens described in these guidelines *(Class I, Level of Evidence: A)*. Other recommendations *(Class IIa, Level of Evidence: C)* listed herein are based largely on in vitro data and consensus opinion and include the following 3 criteria. First, the counting of days of recommended

Table 19.1a Definition of infective endocarditis according to the modified Duke criteria

Definite infective endocarditis

Pathologic criteria

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible IE

- **1 major criterion and 1 minor criterion; or**
- **3 minor criteria**

Rejected

- Firm alternative diagnosis explaining evidence of IE; or
- Resolution of IE syndrome with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE as above

Table 19.1b Definition of terms used in the modified Duke criteria for the diagnosis of infective endocarditis

Major criteria

Blood culture positive for IE

- Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus; or
- Microorganisms consistent with IE from persistently positive blood cultures defined as follows: At least 2 positive cultures of blood samples drawn >12 h apart; or all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
- **Single positive blood culture for *Coxiella burnetii* or anti-phase 1 IgG antibody titer >1 : 800**

Evidence of endocardial involvement

- Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)** defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; new valvular regurgitation (worsening or changing or preexisting murmur not sufficient)

Minor criteria

Predisposition, predisposing heart condition, or IDU

Fever, temperature >38°C

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE

Echocardiographic minor criteria eliminated

Modifications shown in boldface

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

TEE indicates transesophageal echocardiography, and TTE, transthoracic echocardiography.

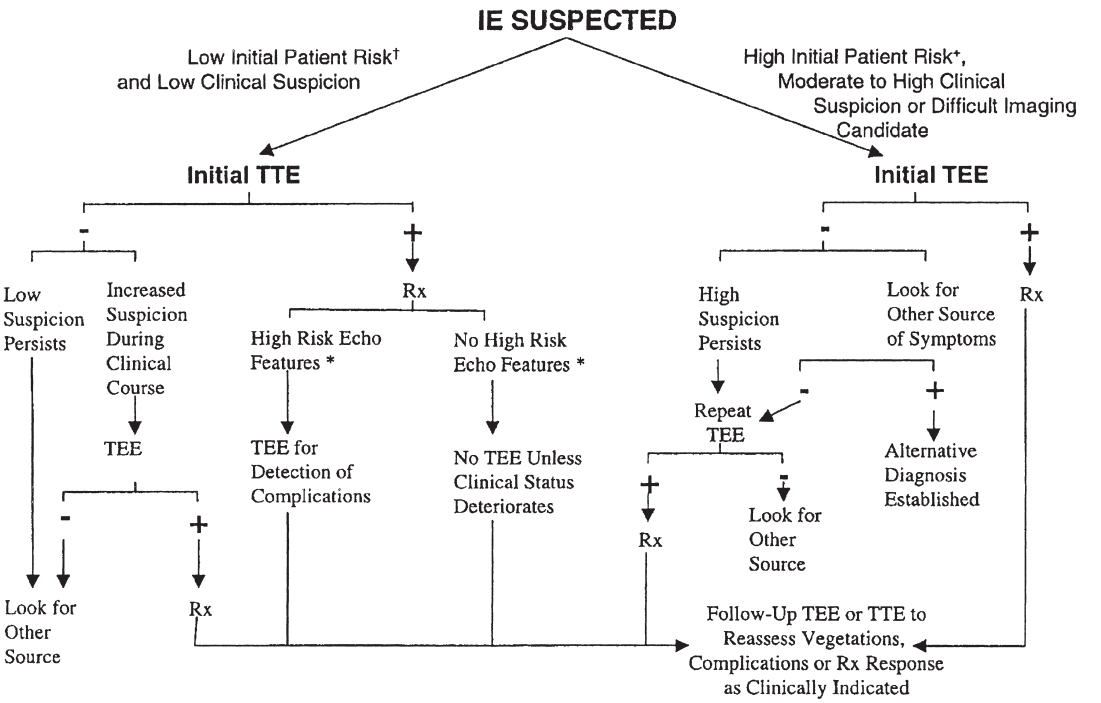

Fig. 19.1 An approach to the diagnostic use of echocardiography (echo).

*High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction.

†For example, a patient with fever and a previously known heart murmur and no other stigmata of IE.

+High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis. Reproduced with permission from Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewitz MH, Newburger JW, Gerber MA, Shulman ST, Pallasch TJ, Gage TW, Ferrieri P. Diagnosis and management of infective endocarditis and its complications. Circulation. 1998;98:2936–2948.

duration of therapy should begin on the first day on which blood cultures were negative in cases in which blood cultures were initially positive. At least two sets of blood cultures should be obtained every 24 to 48 hours until bloodstream infection is cleared. Second, for patients with native valve endocarditis who undergo valve resection with prosthetic valve replacement, the postoperative treatment regimen should be one that is recommended for prosthetic valve treatment rather than one that is recommended for native valve treatment. If the resected tissue is culture positive, then an entire course of antimicrobial therapy is recommended after valve resection. If the resected tissue is culture negative, then the recommended duration of prosthetic valve treatment should be given less the number of days of treatment administered for native valve infection before valve replacement. Third, in regimens that contain combination antimicrobial therapy, it is important to administer agents at the same time or temporally close together to maximize the synergistic killing effect on an infecting pathogen.

Bacteriologic cure rates ≥98% may be anticipated in patients who complete 4 weeks of therapy with parenteral penicillin or ceftriaxone for endocarditis caused by highly penicillin-susceptible viridans group streptococci or *S. bovis* (Table 19.4). Ampicillin is an alternative to penicillin and has been used when penicillin is not available because of supply deficiencies. The addition of gentamicin sulfate to penicillin exerts a synergistic killing effect in vitro on viridans group streptococci and *S. bovis*. The combination of penicillin or ceftriaxone together with gentamicin results in synergistic killing in vivo in animal models of viridans group streptococcal or *S. bovis* experimental endocarditis.

Table 19.2 Use of echocardiography during diagnosis and treatment of endocarditis

Early
Echocardiography as soon as possible (<12 h after initial evaluation)
TEE preferred; obtain TTE views of any abnormal findings for later comparison
TTE if TEE is not immediately available
TTE may be sufficient in small children
Repeat echocardiography
TEE after positive TTE as soon as possible in patients at high risk for complications
TEE 7–10 d after initial TEE if suspicion exists without diagnosis of IE or with worrisome clinical course during early treatment of IE
Intraoperative
Prepump
Identification of vegetations, mechanism of regurgitation, abscesses, fistulae, and pseudoaneurysms
Postpump
Confirmation of successful repair of abnormal findings
Assessment of residual valve dysfunction
Elevated afterload if necessary to avoid underestimating valve insufficiency or presence of residual abnormal flow
Completion of therapy
Establish new baseline for valve function and morphology, ventricular size and function
TTE usually adequate; TEE or review of intraoperative TEE may be needed for complex anatomy to establish new baseline

TEE indicates transesophageal echocardiography, and TTE, transthoracic echocardiography.

Table 19.3 Echocardiographic features that suggest potential need for surgical intervention*

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral leaflet vegetation, particularly with size >10 mm†
≥1 embolic events during first 2 wk of antimicrobial therapy†
Increase in vegetation size despite appropriate antimicrobial therapy†‡
Valvular dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure‡
Heart failure unresponsive to medical therapy‡
Valve perforation or rupture‡
Perivalvular extension
Valvular dehiscence, rupture, or fistula‡
New heart block‡
Large abscess, or extension of abscess despite appropriate antimicrobial therapy‡

* See text for more complete discussion of indications for surgery based on vegetation characterizations.

† Surgery may be required because of risk of embolization.

‡ Surgery may be required because of heart failure or failure of medical therapy.

Recommended antibiotic treatment regimens for IE are described in Tables 19.4–19.14, including drug dose, dosing frequency, route(s) of administration, duration of therapy, and strength of recommendation. Tables 19.4–19.6 provide regimens for IE caused by viridans group streptococci and *Streptococcus bovis*; Tables 19.7 and 19.8, staphylococci; Tables 19.9–19.12, enterococci; Table 19.13, HACEK

Table 19.4 Therapy of native valve endocarditis caused by highly penicillin-susceptible (MIC ≤ 0.12 μg/mL) viridans group streptococci and *Streptococcus bovis*

Regimen	Dosage and route*	Duration, (weeks)	Strength of recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	IA	Preferred in most patients >65 years of age or patients with impairment of 8th cranial nerve function or renal function.
or				
ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	IA	
	*Pediatric dose***: Penicillin 200,000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose			
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	IB	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia, Granulicatella*, or *Gemella* spp. infection. Although it is preferred that gentamicin be given as a single daily dose to adults with IE due to viridans streptococci, as a second option gentamicin can be administered daily in 3 equally divided doses. Gentamicin dosage should be adjusted to achieve a peak serum concentration of 3–4 μg/mL and a trough serum concentration of <1 μg/mL when 3 divided doses are used.
or				
ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	2	IB	
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses	2		
	Pediatric dose: Penicillin 200,000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses‡			
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h unless concentrations in serum are inappropriately low	4	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain a peak (1 h after infusion completed) serum concentration of 30–45 μg/mL and a trough concentration range of 10–15 μg/mL.
	Pediatric dose: 40 mg/kg per 24 h IV in 2–3 equally divided doses			

* Dosages recommended are for patients with normal renal function.

** Pediatric does should nor exceed that of a normal adult.

† Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

‡ Data for once-daily dosing of aminoglycosides for children exist, but there are no data for treatment of IE.

§ Vancomycin dosages should be infused over at least 1 h to reduce risk of the histamine release "red man" syndrome.

IM indicates intramuscular, and MIC, minimal inhibitory concentration.

Table 19.5 Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin (MIC >0.12 μg/ml and ≤0.5 μg/ml)

Regimen	Dosage* and route	Duration, (weeks)	Strength of recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	4	IB	Patients with endocarditis caused by penicillin-resistant (MIC >0.5 μg/mL) strains should be treated with a regimen recommended for enterococcal endocarditis (Table 19.10).
or				
ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	IB	
plus		2		
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses			
	Pediatric dose: Penicillin 300,000 U/24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h unless serum concentrations are inappropriately low	4	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy.
	Pediatric dose: 40 mg/kg/24 h in 2 or 3 equally divided doses			

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should nor exceed that of a normal adult.

† See Table 19.4 for appropriate dosage of gentamicin.

‡ See Table 19.4 for appropriate dosage of vancomycin.

IM indicates intramuscular, and MIC, minimum inhibitory concentration.

microorganisms; and Table 19.14, culture-negative IE, including *Bartonella* endocarditis. With few exceptions, antibiotic treatment is prolonged, bactericidal, administered parenterally, and given in high dosages. Because complications of IE are frequent and the antimicrobial agents used to treat IE may be associated with adverse effects, patients must be monitored closely by an experienced team of clinicians.

A dramatic increase in resistance to antibiotics among the most common causes of IE is a major reason for updating these recommendations. Multidrug resistance is now commonly described among isolates of streptococcal, staphylococcal, and enterococcal species that cause IE. In addition, many of the Gram-negative bacteria that cause IE have become more drug resistant. Increasing drug resistance has occurred among "community-acquired" isolates such as HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) microorganisms, *Salmonella* species, and Enterobacteriaceae, as well as among nosocomial isolates such as *Pseudomonas* species. More data are needed to define the optimal treatment regimens for IE caused by multidrug-resistant *Streptococcus pneumoniae*, vancomycin-resistant strains of *Enterococcus faecium*, and multidrug-resistant *Staphylococcus aureus*. In addition, new information has prompted a reexamination of recommendations for the duration of therapy for IE. For example, data from Sweden suggest that in combination with a cell wall-active antibiotic for treatment of IE resulting from enterococci, the duration of aminoglycoside administration may be limited to only the first 2 weeks rather than the

Table 19.6 Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis**

Regimen	Dosage and route	Duration, (weeks)	Strength of recommendation	Comments
Penicillin-susceptible strain (minimum inhibitory concentration ≤0.12 μg/mL)				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IB	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with a highly susceptible strain; gentamicin therapy should not be administered to patients with a creatinine clearance of <30 mL/min.
or				
ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
with or without				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses *Pediatric dose***: Penicillin 300,000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg IV/IM once daily; gentamicin 3 mg/kg/24 h IV/IM, in 1 dose or 3 equally divided doses	2		
Vancomycin hydrochloride‡	30 mg/kg/24 h IV in 2 equally divided doses *Pediatric dose*: 40 mg/kg/24 h IV or in 2 or 3 equally divided doses	6	IB	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone.
Penicillin relatively or fully resistant strain (minimum inhibitory concentration >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IB	
or				
ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses *Pediatric dose*: Penicillin 300,000 U/kg per 24 h IV in 4–6 equally divided doses	6		
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses *Pediatric dose*: 40 mg/kg per 24 h IV in 2 or 3 equally divided doses	6	IB	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone.

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† See Table 19.4 for appropriate dosage of gentamicin.

‡ See text and Table 19.4 for appropriate dosage of vancomycin.

IM indicates intramuscular.

Table 19.7 Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials*

Regimen	Dosage and route	Duration	Strength of recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin† **or** oxacillin ***with***	12 g/24 h IV in 4–6 equally divided doses	6 wk	IA	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, i.e., 2 wk (see text).
optional addition of gentamicin sulfate‡	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses *Pediatric dose***: Nafcillin or oxacillin 200 mg/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses	3–5 d		Clinical benefit of aminoglycosides has not been established.
For penicillin-allergic (non-anaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin ***with***	6 g/24 h IV in 3 equally divided doses	4–6 wk 3–5 d	IB	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.§
optional addition of gentamicin sulfate‡	3 mg/kg/24 h IV/IM in 2 or 3 equally divided doses *Pediatric dose*: Cefazolin 100 mg/kg per 24 h IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			Clinical benefit of aminoglycosides has not been established.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg/24 h IV in 2 equally divided doses *Pediatric dose*: 40 mg/kg/24 h IV in 2 or 3 equally divided doses	6 wk	IB	Adjust vancomycin dosage to achieve 1-h serum concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL. See text for alternatives to vancomycin.

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† Penicillin G 24 million U/24 h may be used in place of nafcillin or oxacillin if strain is penicillin-susceptible (minimum inhibitory concentration ≤0.1 μg/mL).

‡ Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 19.4 for appropriate dosage of gentamicin.

§ For specific dosing adjustment and issues concerning vancomycin, see Table 19.4 footnotes.

IM indicates intramuscular.

Table 19.8 Therapy for prosthetic valve endocarditis caused by staphylococci*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	IB	Penicillin G 24 million U/24 h in 4–6 equally dived doses may be used in place of nafcillin or oxacillin if strain is penicillin-susceptible (MIC ≤0.1 μg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 19.4 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins.
plus				
rifampin	900 mg IV/PO in 3 equally divided doses	≥6		
plus				
gentamicin†	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		
	*Pediatric** dose*: Nafcillin or oxacillin 200 mg/kg per 24 h IV in 4–6 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Oxacillin-resistant strains				
Vancomycin	30 mg/kg per 24 h in 2 equally divided doses	≥6	IB	Adjust vancomycin to achieve 1-hour serum concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL.
plus				
rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
plus				
gentamicin†	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		If strains are resistant to gentamicin, a fluoroquinolone may be used if the strain is susceptible.
	Pediatric dose: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses (up to the adult dose); gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses	2		

*Dosages recommended are for patients with normal renal function.

**Pediatric dose should not exceed that of a normal adult.

†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 19.4 for appropriate dosage of gentamicin.

MIC indicates minimum inhibitory concentration; PO, oral; and IM, intramuscular.

entire 4 to 6 weeks of therapy with a cell wall-active agent and no decrease in cure rates.

Despite advances in diagnostic techniques, (blood) culture-negative endocarditis remains a clinical conundrum among IE cases. Patients with culture-negative endocarditis can be divided into two categories: those with negative blood cultures associated with recent antibiotic therapy and those infected with microorganisms that are difficult to grow in routinely used blood culture media. The epidemiological clues listed in Table 19.15 may be helpful for determining the most appropriate

Table 19.9 Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	4–6	IA	Native valve: 4-wk therapy recommended for patients with symptoms of illness ≤3 mo; 6-wk therapy recommended for patients with symptoms >3 mo.
or				
a queous crystalline penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6	IA	Prosthetic valve or other prosthetic cardiac material: A minimum of 6 wk of therapy recommended.
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	4–6		
	*Pediatric dose***: Ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; penicillin 300,000 U/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin.
plus		6		
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses			6-wk of vancomycin therapy recommended because of decreased activity against enterococci.
	Pediatric dose: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† The dosage of gentamicin should be adjusted to achieve a peak serum concentration of 3–4 μg/mL and a trough concentration of <1 μg/mL. See Table 19.4 for appropriate dosage of gentamicin.

‡ See Table 19.4 for appropriate dosing of vancomycin.

IM indicates intramuscular.

antibiotic regimen for the individual patient with culture-negative endocarditis.

Complications and their treatment

Surgical therapy

Patients with IE and CHF, irrespective of the mechanism, should be immediately evaluated for possible surgical therapy *(Class I, Level of Evidence: B)*. Despite a higher operative mortality rate in patients with CHF than in those without CHF, patients with IE who have CHF and undergo valve surgery have a substantially reduced mortality rate compared with those treated with medical therapy alone. The incidence of reinfection of newly implanted valves in patients with active IE is ≈2% to 3% and is far less than the mortality rate for IE and CHF without surgical therapy, which can be as high as 51%. Surgical approaches to CHF caused by different mechanisms are discussed in the section on CHF.

Table 19.10 Therapy for native or prosthetic valve enterococcal endocarditis caused by stains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Ampicillin sodium ***or***	12 g/24 h IV in 6 equally divided doses	4–6	IA	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for patients with symptoms >3 mo.
aqueous crystalline penicillin G sodium ***plus***	24 million U/24 h IV continuously or in 6 equally divided doses	4–6	IA	
streptomycin sulfate†	15 mg/kg/24 h IV/IM in 2 equally divided doses *Pediatric dose***: Ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; penicillin 300,000 U/kg per 24 h IV in 4–6 equally divided doses; streptomycin 20–30 mg/kg per 24 h IV/IM in 2 equally divided doses	4–6		Prosthetic valve or other prosthetic cardiac material: A minimum of 6 weeks of therapy is recommended.
Vancomycin hydrochloride‡ ***plus***	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin.
streptomycin sulfate†	15 mg/kg per 24 h IV/IM in 2 equally divided doses *Pediatric dose*: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; streptomycin 20–30 mg/kg per 24 h IV/IM in 2 equally divided doses	6		

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† See text for appropriate dosing of streptomycin.

‡ See text and Table 19.4 for appropriate dosing of vancomycin.

IM indicates intramuscular.

Other clinical situations in which surgical intervention should be considered are fungal IE, infection with aggressive antibiotic-resistant bacteria or bacteria that respond poorly to antibiotics, left-sided IE caused by Gram-negative bacteria such as *S. marcescens* and *Pseudomonas* species, persistent infection with positive blood cultures after 1 week of antibiotic therapy, or one or more embolic events during the first 2 weeks of antimicrobial therapy *(Class I, Level of Evidence: B)*.

Consideration of surgical intervention also is warranted when there is echocardiographic evidence of

Table 19.11 Therapy for native or prosthetic valve enterococcal endocarditis caused by strains resistant to penicillin and susceptible to aminoglycoside and vancomycin*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
β-Lactamase–producing strain				
Ampicillin-sulbactam	12 g/24 h IV in 4 equally divided doses	6	IIaC	Unlikely that the strain will be susceptible to gentamicin; if strain is gentamicin resistant, then >6 wk of ampicillin-sulbactam therapy will be needed.
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	*Pediatric dose***: Ampicillin-sulbactam 300 mg/kg per 24 h IV in 4 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIaC	Vancomycin therapy recommended only for patients unable to tolerate ampicillin-sulbactam.
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	Pediatric dose: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Intrinsic penicillin resistance				
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIaC	Consultation with a specialist in infectious diseases recommended.
plus				
gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	Pediatric dose: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† See text and Table 19.4 for appropriate dosing of gentamicin.

‡ See Table 19.4 for appropriate dosing of vancomycin.

IM indicates intramuscular.

Table 19.12 Therapy for native or prosthetic valve enterococcal endocarditis caused by strains resistant to penicillin, aminoglycoside, and vancomycin*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
E. faecium				Patients with endocarditis caused by these strains should be treated in consultation with an infectious diseases specialist; cardiac valve replacement may be necessary for bacteriologic cure; cure with antimicrobial therapy alone may be <50%; severe, usually reversible thrombocytopenia may occur with use of linezolid, especially after 2 wk of therapy; quinupristin-dalfopristin is only effective against *E. faecium* and can cause severe myalgias, which may require discontinuation of therapy; only small no. of patients have reportedly been treated with imipenem/cilastatin-ampicillin or ceftriaxone + ampicillin.
Linezolid	1200 mg/24 h IV/PO in 2 equally divided doses	≥8	IIaC	
or				
quinupristin-dalfopristin	22.5 mg/kg per 24 h IV in 3 equally divided doses	≥8		
E. faecalis				
Imipenem/cilastatin	2 g/24 h IV in 4 equally divided doses	≥8	IIbC	
plus				
ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
or				
ceftriaxone sodium	4 g/24 h IV/IM in 2 equally divided doses	≥8	IIbC	
plus				
ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
	*Pediatric dose***: Linezolid 30 mg/kg per 24 h IV/PO in 3 equally divided doses; quinupristin-dalfopristin 22.5 mg/kg per 24 h IV in 3 equally divided doses; imipenem/cilastatin 60–100 mg/kg per 24 h IV in 4 equally divided doses; ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in two equally divided doses			

Decreasing order of preference based on published data.

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

PO indicates oral, and IM, intramuscular.

valve dehiscence, perforation, rupture, or fistula, or a large perivalvular abscess *(Class I, Level of Evidence: B)*. Other echocardiographic findings that indicate the possible need for surgery are anterior mitral leaflet vegetation (particularly with size >10 mm) or persistent vegetation after systemic embolization *(Class IIa, Level of Evidence: B)* and an increase in vegetation size despite appropriate antimicrobial therapy (*Class IIb, Level of Evidence: C*; Table 19.3). Decision making regarding the role of surgical intervention to prevent systemic embolization is complex and must be individualized to the patient. Benefit is greatest in the early phase of IE, when embolic rates are highest and other predictors of a complicated course (e.g., recurrent embolization and prosthetic valve endocarditis) are present. The greatest risk of

Table 19.13 Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Ceftriaxone sodium ***or***	2 g/24 h IV/IM in 1 dose*	4	IB	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
ampicillin-sulbactam† ***or***	12 g/24 h IV in 4 equally divided doses	4	IIaB	
ciprofloxacin†‡	1000 mg/24 h PO or 800 mg/24 h IV in 2 equally divided doses *Pediatric dose***: Ceftriaxone 100 mg/kg per 24 h IV/IM once daily; ampicillin-sulbactam 300 mg/kg per 24 h IV divided into 4 or 6 equally divided doses; ciprofloxacin 20–30 mg/kg per 24 h IV/PO in 2 equally divided doses	4	IIbC	Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients <18 years of age. Prosthetic valve: Patients with endocarditis involving a prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wk.

* Patients should be informed that IM injection of ceftriaxone is painful.

** Pediatric dose should not exceed that of a normal adult.

† Dosage recommended for patients with normal renal function.

‡ Fluoroquinolones are highly active *in vitro* against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal.

IM indicates intramuscular, and PO, oral.

embolization appears to occur with vegetations >10 mm in diameter occurring on the anterior mitral leaflet and during the first 1 to 2 weeks of therapy.

Congestive heart failure

Many studies during the past three decades have demonstrated that among the complications of IE, CHF has the greatest impact on prognosis. Moderate to severe CHF was identified as one of five baseline features that were independently associated with 6-month mortality in an investigation to validate a prognostic classification system for adults with complicated left-sided native valve IE. In native valve IE, acute CHF occurs more frequently in aortic valve infections (29%) than with mitral (20%) or tricuspid disease (8%). In addition, the degree of tolerance of CHF is valve dependent, with acute aortic regurgitation being least tolerant and acute tricuspid regurgitation most tolerant. The tolerance for acute mitral regurgitation is intermediate. CHF may develop acutely from perforation of a native or bioprosthetic valve leaflet, rupture of infected mitral chordae, valve obstruction by bulky vegetations, or sudden intracardiac shunts from fistulous tracts or prosthetic dehiscence. Mitral valve preclosure that can be detected by both physical examination and echocardiography should be screened for in each case.

Risk of embolization

Systemic embolization occurs in 22% to 50% of cases of IE. Emboli often involve major arterial beds,

Table 19.14 Therapy for culture-negative endocarditis including *Bartonella* endocarditis*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Native valve				
Ampicillin-sulbactam	12 g/24 h IV in 4 equally divided doses	4–6	IIbC	Patients with culture-negative endocarditis should be treated with consultation with an infectious diseases specialist.
plus				
gentamicin sulfate†	3 mg/kg/24 h IV/IM in 3 equally divided doses	4–6		
Vancomycin‡	30 mg/kg per 24 h IV in 2 equally divided doses	4–6	IIbC	Vancomycin recommended only for patients who are unable to tolerate penicillins.
plus				
gentamicin sulfate	3 mg/kg/24 h IV/IM in 3 equally divided doses	4–6		
plus				
ciprofloxacin	1000 mg/24 h PO or 800 mg/24 h IV in 2 equally divided doses	4–6		
	*Pediatric dose***: Ampicillin-sulbactam 300 mg/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; vancomycin 40 mg/kg per 24 h in 2 or 3 equally divided doses; ciprofloxacin 20–30 mg/kg per 24 h IV/PO in 2 equally divided doses			
Prosthetic valve (early, ≤1 y)				
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIbC	
plus				
gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
plus				
cefepime	6 g/24 h IV in 3 equally divided doses	6		
plus				
rifampin	900 mg/24 h PO/IV in 3 equally divided doses	6		
	Pediatric dose: Vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; cefepime 150 mg/kg per 24 h IV in 3 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 3 equally divided doses			

Table 19.14 *Continued*

Regimen	Dosage and route	Duration (weeks)	Strength of recommendation	Comments
Prosthetic valve (late, >1 y)				
		6	IIibC	Same regimens as listed above for native valve endocarditis with the addition of rifampin.
Suspected *Bartonella*, culture negative				
Ceftriaxone sodium ***plus***	2 g/24 h IV/IM in 1 dose	6	IIaB	Patients with *Bartonella* endocarditis should be treated in consultation with an infectious diseases specialist.
gentamicin sulfate ***with/without***	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
doxycycline	200 mg/24 h IV/PO in 2 equally divided doses	6		
Documented *Bartonella*, culture positive				
Doxycycline ***plus***	200 mg/24 h IV or PO in 2 equally divided doses	6	IIaB	If gentamicin cannot be given, then replace it with rifampin, 600 mg/24 h PO/IV in 2 equally divided doses.
gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
	Pediatric dose: Ceftriaxone 100 mg/kg per 24 h IV/IM once daily; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; doxycycline 2–4 mg/kg per 24 h IV/PO in 2 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 2 equally divided doses			

* Dosages recommended are for patients with normal renal function.

** Pediatric dose should not exceed that of a normal adult.

† See text and Table 19.4 for appropriate dosing of gentamicin.

‡ See Table 19.4 for appropriate dosing of vancomycin.

IM indicates intramuscular, and PO, oral.

including the lungs, coronary arteries, spleen, bowel, and extremities. Up to 65% of embolic events involve the central nervous system, and >90% of central nervous system emboli lodge in the distribution of the middle cerebral artery. The highest incidence of embolic complications is seen with aortic and mitral valve infections and in IE caused by *S. aureus*, *Candida*, HACEK, and *Abiotrophia* organisms. Emboli can occur before diagnosis, during therapy, or after therapy is completed, although most emboli occur within the first 2 to 4 weeks of antimicrobial therapy.

Periannular extension of infection

Extension of IE beyond the valve annulus predicts a higher mortality rate, more frequent development of CHF, and more frequent cardiac surgery.

Table 19.15 Epidemiological clues in etiologic diagnosis of culture-negative endocarditis

Epidemiological feature	Common microorganism(s)
Injection drug use	*S. aureus*, including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus* Coagulase-negative staphylococci Fungi Aerobic gram-negative bacilli *Corynebacterium* species
Genitourinary disorders, infection, manipulation, including pregnancy, delivery, and abortion	*Enterococcus* sp. Group B streptococci (*S. agalactiae*) *Listeria monocytogenes* Aerobic gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S. aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci "Nutritionally variant streptococci" *Abiotrophia defectiva* *Granulicatella* species *Gemella* species HACEK organisms
Alcoholism, cirrhosis	*Bartonella* sp. *Aeromonas* sp. *Listeria* sp. *S. pneumoniae* β-Hemolytic streptococci
Burn patients	*S. aureus* Aerobic gram-negative bacilli, including *P. aeruginosa* Fungi
Diabetes mellitus	*S. aureus* β-Hemolytic streptococci *S. pneumoniae*
Early (≤1 y) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Aerobic gram-negative bacilli Fungi *Corynebacterium* sp. *Legionella* sp.

Table 19.15 *Continued*

Epidemiological feature	Common microorganism(s)
Late (>1 y) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Viridans group streptococci *Enterococcus* sp. Fungi *Corynebacterium* sp.
Dog-cat exposure	*Bartonella* sp. *Pasteurella* sp. *Capnocytophaga* sp.
Contact with contaminated milk or infected farm animals	*Brucella* sp. *Coxiella burnetii* *Erysipelothrix* sp.
Homeless, body lice	*Bartonella* sp.
AIDS	*Salmonella* sp. *S. pneumoniae* *S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid organ transplant	*S. aureus* *Aspergillus fumigatus* *Enterococcus* sp. *Candida* sp.
Gastrointestinal lesions	*S. bovis* *Enterococcus* sp. *Clostridium septicum*

Perivalvular cavities form when annular infections break through and spread into contiguous tissue. In native aortic valve IE, this generally occurs through the weakest portion of the annulus, which is near the membranous septum and atrioventricular node. The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a common sequela. Periannular extension has been reported to occur in up to 40% of cases of native valve IE (complicating aortic IE more commonly than mitral or tricuspid IE) and up to 100% of patients with prosthetic valve IE. Perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the usual primary site of infection. Most periannular infections involving the mitral area are associated with prosthetic mitral valves.

Mycotic aneurysms

Mycotic aneurysms (MAs) are uncommon complications of IE that result from septic embolization of vegetations to the arterial vasa vasorum or the intraluminal space, with subsequent spread of infection through the intima and outward through the vessel wall. Arterial branching points favor the impaction of emboli and are the most common sites of development of MAs. MAs caused by IE occur most frequently in the intracranial arteries, followed by the visceral arteries and the arteries of the upper and lower extremities.

Outpatient therapy

Outpatient parenteral antibiotic therapy (OPAT) has been shown to be efficacious, safe, and cost-effective for a variety of chronic infections that require prolonged parenteral therapy in selected patients who otherwise do not require hospitalization. Antibiotic regimens recommended for endocarditis require ≥2 weeks of therapy, usually by the intravenous route. Absorption of orally administered antimicrobial agents may be unreliable and is generally not recommended for the treatment of endocarditis, especially during the initial phase of therapy. Economic and other pressures have encouraged shorter hospital stays for endocarditis patients resulting in use of shorter courses of intravenous antimicrobial therapy for selected indications or in development of regimens for outpatient administration of intravenous antibiotic therapy.

The following criteria are essential for an effective OPAT program:

- A reliable support system at home and easy access to a hospital for prompt reevaluation by an experienced physician should a complication develop, such as recurrence of fever, symptoms of a cardiac arrhythmia, CHF, or a neurological event.
- Regular visits by a home infusion nurse who carefully monitors the patient for early detection of complications, failure to respond to therapy, problems with adherence to therapy, or complications (e.g., infection, leakage, displacement) directly related to the antibiotics or intravenous access.
- Regular visits with an experienced physician to assess clinical status while receiving OPAT.

Care at completion of treatment

Short-term follow-up

A majority of patients with IE are cured with appropriate medical and, if necessary, surgical treatment. Before completing antimicrobial therapy, undergo TTE *(Class IIb, Level of Evidence: C)* may be considered to establish a new baseline for subsequent comparison (Table 19.16). A referral to a program to assist in cessation of drug use should be made for IDU patients. Patients should be educated about the signs of endocarditis and urged to seek immediate medical attention should they occur. A thorough dental evaluation should be obtained and all active sources of oral infection should be eradicated. All catheters used to infuse antimicrobial treatment should be promptly removed at the end of therapy. Blood cultures should be obtained if fever develops and before an antibiotic is administered.

Long-term follow-up

Months to years after completion of medical therapy for IE, patients need ongoing observation and education regarding recurrent infection and delayed onset of worsening valvular dysfunction (Table 19.16). Ongoing daily dental hygiene should be stressed, with serial evaluations by a dentist who is familiar with this patient population. Patients should be questioned about the symptoms of decreased cardiac output and CHF. A thorough cardiac examination will be needed. Additional evaluations with TTE will be necessary in selected patients with positive findings from history and physical examination. Patients must be reminded to seek immediate medical evaluation for fever (Table 19.16). This is

Table 19.16 Care during and after completion of antimicrobial treatment

Initiate before or at completion of therapy
Obtain transthoracic echocardiogram to establish new baseline
Drug rehabilitation referral for patients who use illicit injection drugs
Educate regarding signs of endocarditis, need for antibiotic prophylaxis for certain dental/surgical/invasive procedures
Thorough dental evaluation and treatment if not performed earlier in evaluation
Prompt removal of IV catheter at completion of antimicrobial therapy
Short-term follow-up
Obtain at least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Physical examination for evidence of congestive heart failure
Evaluate for toxicity resulting from current/previous antimicrobial therapy
Long-term follow-up
Obtain at least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Evaluation of valvular and ventricular function (echocardiography)
Scrupulous oral hygiene and frequent dental professional office visits

necessary because IE can mimic panoply of febrile illnesses. Antibiotic therapy should not be initiated for treatment of undefined febrile illnesses without obtaining previous blood cultures. Antibiotics prescribed for nonspecific or unproved febrile syndromes are the major cause of (blood) culture-negative endocarditis and should be strongly discouraged.

Guidelines for the prevention of infective endocarditis

Infective endocarditis (IE) remains an uncommon but life-threatening infection. Despite advances in diagnosis, antimicrobial therapy, surgical techniques, and management of complications, patients with IE still have high morbidity and mortality rates related to this condition. In recent years many authorities, societies, and authors of peer-reviewed published studies, have questioned the efficacy of antimicrobial prophylaxis to prevent IE in patients who undergo a dental, gastrointestinal (GI), or genitourinary (GU) tract procedure. Accordingly, the AHA commissioned a writing group, led by members of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, to revise their 1997 prophylaxis guidelines. The writing group was selected for their expertise in prevention and treatment of infective endocarditis, with liaison members representing the American Dental Association (ADA), the Infectious Diseases Society of America, and the American Academy of Pediatrics. The document was reviewed by peer reviewers appointed by the AHA and the ADA and by a group of international experts on IE. The Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease will carefully review future published data and further revisions to the present document will be based on relevant studies.

The writing group conducted a comprehensive literature review using PubMed/MEDLINE database searches from 1950 to 2006 for English-language papers regarding procedure-related bacteremia and infective endocarditis, in vitro susceptibility data of the most common microorganisms that cause infective endocarditis, results of prophylactic studies in animal models of experimental endocarditis, and retrospective and prospective studies of prevention of infective endocarditis.

History of AHA Statements on prevention of IE

The AHA has made recommendations for the prevention of IE for more than 50 years. Table 19.17 shows a summary of the documents published from 1955 to 1997. One can see the evolution in prophylaxis recommendations over these 50 years, from multi-day administration of antibiotics (including some parental administration) to single day oral dosing. Up through the 1997 recommendations, the rationale for prophylaxis was based largely on expert opinion and what seemed to be a rational and prudent attempt to prevent a life-threatening infection. On the basis of the ACC and AHA Task Force on Practice Guidelines' evidence-based grading system for ranking recommendations, the recommendations in the AHA documents published during the past 50 years would be Class IIb, LOE C. Accordingly, the basis for recommendations for IE prophylaxis was not well established, and the quality of evidence was limited to a few case-control studies or was based on expert opinion, clinical experience, and descriptive studies that utilized surrogate measures of risk.

During its deliberations on the 2007 guidelines, the Writing Group established these primary reasons for revising the recommendations for IE prophylaxis:

- IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU tract procedure.
- Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract, or GU tract procedure.
- The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.
- Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.

Dental procedures and IE

Although it has long been assumed that dental procedures may cause IE in patients with underlying cardiac risk factors and that antibiotic prophylaxis is effective, scientific proof is lacking to support

Table 19.17 Summary of 9 iterations of AHA-recommended antibiotic regimens from 1955 to 1997 for dental/respiratory tract procedures*

Year	Primary regimens for dental procedures
1955	Aqueous penicillin 600,000 U and procaine penicillin 600,000 U in oil containing 2% aluminum monostearate administered IM 30 minutes before the operative procedure
1957	For 2 days before surgery, penicillin 200,000 to 250,000 U by mouth 4 times per day. On day of surgery, penicillin 200,000 to 250,000 U by mouth 4 times per day and aqueous penicillin 600,000 U with procaine penicillin 600,000 U IM 30 to 60 minutes before surgery. For 2 days after, 200,000 to 250,000 U by mouth 4 times per day.
1960	Step I: prophylaxis 2 days before surgery with procaine penicillin 600,000 U IM on each day Step II: day of surgery: procaine penicillin 600,000 U IM supplemented by crystalline penicillin 600,000 U IM 1 hour before surgical procedure Step III: for 2 days after surgery: procaine penicillin 600,000 U IM each day
1965	Day of procedure: procaine penicillin 600,000 U, supplemented by crystalline penicillin 600,000 U IM 1 to 2 hours before the procedure For 2 days after procedure: procaine penicillin 600,000 U IM each day
1972	Procaine penicillin G 600,000 U mixed with crystalline penicillin G 200,000 U IM 1 hour before procedure and once daily for the 2 days after the procedure
1977	Aqueous crystalline penicillin G (1,000,000 U IM) mixed with procaine penicillin G (600,000 U IM) 30 minutes to 1 hour before procedure and then penicillin V 500 mg orally every 6 hours for 8 doses.
1984	Penicillin V 2 g orally 1 hour before, then 1 g 6 hours after initial dose
1990	Amoxicillin 3 g orally 1 hour before procedure, then 1.5 g 6 hours after initial dose
1997	Amoxicillin 2 g orally 1 hour before procedure

IM indicates intramuscularly.

*These regimens were for adults and represented the initial regimen listed in each version of the recommendations. In some versions, >1 regimen was included.

these assumptions. The collective published evidence suggests that of the total number of cases of IE that occur annually, it is likely that an exceedingly small number are caused by bacteremia-producing dental procedures. Accordingly, only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if it were 100% effective. The vast majority of cases of IE caused by oral microflora most likely result from random bacteremias caused by routine daily activities, such as chewing food, tooth brushing, flossing, use of toothpicks, use of water irrigation devices, and other activities. The presence of dental disease may increase the risk of bacteremia associated with these routine activities. There should be a shift in emphasis away from a focus on a dental procedure and antibiotic prophylaxis toward a greater emphasis on improved access to dental care and oral health in patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE and those conditions that predispose to the acquisition of IE.

Table 19.18 Dental procedures for which endocarditis prophylaxis is reasonable for patients in Table 19.17

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*

*The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

In situations where prophylaxis is recommended, it should be used for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (Table 19.18).

Cardiac conditions and endocarditis

Previous AHA guidelines categorized underlying cardiac conditions associated with the risk of IE as

those with high risk, moderate risk, and negligible risk and recommended prophylaxis for patients in the high- and moderate-risk categories. For the present guidelines on prevention of IE, the Committee considered three distinct issues: (1) What underlying cardiac conditions over a lifetime have the highest predisposition to the acquisition of endocarditis? (2) What underlying cardiac conditions are associated with the highest risk of adverse outcome from endocarditis? (3) Should recommendations for IE prophylaxis be based on either or both of these two conditions?

In a major departure from previous AHA guidelines, the writing group no longer recommends IE prophylaxis based solely on an increased lifetime risk of acquisition of IE. Rather, prophylaxis is recommended for patients with highest risk of adverse outcome from endocarditis (Table 19.19). It is noteworthy that patients with the conditions listed in Table 19.19 are also among those patients with the highest lifetime risk of acquisition of endocarditis. No published data demonstrate convincingly that the administration of prophylactic antibiotics prevents IE associated with bacteremia from an invasive procedure. We cannot exclude the possibility that there may be an exceedingly small number of cases of IE that could be prevented by prophylactic antibiotics in patients who undergo an invasive procedure. However, if prophylaxis is effective, such therapy should be restricted to those patients with the highest risk of adverse outcome from IE who would derive the greatest benefit from prevention of IE.

Table 19.19 Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
Congenital heart disease (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Prophylaxis for dental procedures in patients with cardiac conditions associated with the highest risk of adverse outcome from endocarditis

In patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE, prophylaxis for dental procedures is reasonable, even though we acknowledge that its effectiveness is unknown *(Class IIa, LOE B)*.

Regimens for respiratory tract procedures

A variety of respiratory tract procedures reportedly cause transient bacteremia with a wide array of microorganisms; however, no published data conclusively demonstrate a link between these procedures and IE. Antibiotic prophylaxis with a regimen listed in Table 19.20 is reasonable *(Class IIa, LOE C)* for patients with the conditions listed in Table 19.19 who undergo an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy. We do not recommend antibiotic prophylaxis for bronchoscopy unless the procedure involves incision of the respiratory tract mucosa.

Recommendations for GI or GU tract procedures

The administration of prophylactic antibiotics solely to prevent endocarditis is not recommended for patients who undergo GU or GI tract procedures, including diagnostic esophagogastroduodenoscopy or colonoscopy *(Class III, LOE B)*. This is in contrast to previous AHA guidelines that listed GI or GU tract procedures for which IE prophylaxis was recommended and those for which prophylaxis was not recommended.

Regimens for procedures on infected skin, skin structure, or musculoskeletal tissue

These infections are often polymicrobial, but only staphylococci and β-hemolytic streptococci are likely to cause IE. For patients with the conditions

Ongoing trials, future directions in the management and prevention of IE

Following publication of the management guidelines, clinical data have been published and support the use of daptomycin as an alternative treatment option in patients with right-sided IE due to *S. aureus*. Results of additional study with double beta-lactam therapy for enterococcal endocarditis are now available. Recent investigations have prompted a re-examination of anti-platelet therapy as an adjunct to antimicrobial treatment.

Due to the interest in the prevention of dental caries caused by viridans group streptococci, several vaccines are being developed. It is conceivable that one or more of these vaccines could prove helpful in the prevention of IE in high risk patients who are immunized. Work in an animal model of endocarditis suggests that infection prevention by this modality is feasible.

A placebo-controlled, multicenter, randomized, double-blinded study to evaluate the efficacy of IE prophylaxis in patients who undergo a dental, GI, or GU tract procedure has not been done. Such a study would require a large number of patients per treatment group and standardization of the specific invasive procedures and the patient populations. This type of study would be necessary to definitively answer long-standing unresolved questions regarding the efficacy of IE prophylaxis. It is hoped that the current IE prophylaxis guidelines will stimulate additional studies on the prevention of IE.

Table 19.20 Regimens for a dental procedure

Situation	Agent	Regimen: single dose 30 to 60 min before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	Or		
	cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin*†	2 g	50 mg/kg
	Or		
	clindamycin	600 mg	20 mg/kg
	Or		
	azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
	Or		
	clindamycin†	600 mg IM or IV	20 mg/kg IM or IV

IM indicates intramuscular; IV, intravenous.

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

listed in Table 19.19 who undergo a surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue, it may be reasonable that the therapeutic regimen administered for treatment of the infection contain an agent active against staphylococci and β-hemolytic streptococci, such as an antistaphylococcal penicillin or a cephalosporin (Table 19.20 for dosage; *Class IIb, LOE C*). Vancomycin or clindamycin may be administered to patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant strain of staphylococcus.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

20 Cardiac CT Imaging

Matthew J. Budoff and Allen J. Taylor

Scientific Statement on Cardiac CT – 2006
Coronary calcium scanning
Summary from the AHA Scientific Statement
Coronary calcium scanning
Additional statements/guidelines related to coronary artery calcium
ACC/AHA Expert Consensus Document on coronary calcium
Comparison with European Guidelines
Cardiac CT Angiography – Scientific Statement 2006
Hybrid imaging with CT and nuclear imaging
Recommendations
CT angiography
Hybrid scanning (nuclear and CT)
Ongoing trials
Future directions
Tracking progression of subclinical atherosclerosis
Conclusions
2008 Statement on noninvasive coronary artery imaging: MR angiography and multi-detector CT angiography
Specific recommendations for use of CTA and MRA
ACCF/AHA 2007 clinical competence statement on vascular imaging with computed tomography and magnetic resonance
CT angiography
Specific applications
Magnetic resonance angiography

Scientific Statement on Cardiac CT – 2006 [1]

During the past decade, there has been a progressive increase in the clinical use of cardiac computed tomography scanning to identify and quantify the amount of coronary artery calcified plaque (CACP), leading to both much interest and scrutiny. On the basis of the substantial validation data, electron beam computed tomography (EBCT) remains the reference standard for CACP measurement. The technology of cardiac computed tomography has undergone rapid transformation in recent years such that new scanners with sub-second image acquisition multirow capability have been studied and now multidetector computed tomography (MDCT) is suggested as an alternative approach to EBCT to detect coronary calcification which may broaden the availability of CACP detection as a consequence of the greater availability of such scanners. Thus, although coronary calcification can be quantified and calcium scores can be related to extent and severity of atherosclerotic disease and its prognosis, misuse or abuse of these methods as a broad-based "screening" tool has created considerable controversy.

This statement reviews the scientific data for cardiac computed tomography (CT) related to imaging of coronary artery disease and atherosclerosis. Cardiac CT is a computed tomographic imaging technique that accounts for cardiac motion, typically through the use of ECG gating. The utility and limitations of generations of cardiac CT systems are reviewed in this statement with emphasis on CT measurement of coronary artery disease and coronary artery calcified plaque (CACP) and noncalcified plaque (CANCP).

The committee directing the generation of this document was composed of representatives of the AHA, Society of Atherosclerosis Imaging and Prevention (SAI-P) and Society of Cardiovascular Computed Tomography. The document was reviewed by individuals nominated by these organizations. This statement updates the 2000 scientific statement on Electron Beam Computed

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Table 20.1 Characteristics and Risk Ratio for Follow-Up Studies Using EBCT

Author	No.	Mean Age, y	Follow-Up Duration, y	Calcium Score Cutoff	Comparative Group for RR Calculation	Risk Factor Assessment	Relative Risk Ratio
EBCT studies in symptomatic cohorts							
Georglou[93]	192	53	4.2	Median*	Below median	Measured	13.1
Detrano[123]	491	57	2.5	Top quartile	Bottom quartile	Self-reported	10.8
Keelan[124]	288	56	6.9	Median (>480)	Below median	Measured	3.2
Moehlenkamp[125]	150	63	5	CACP >1000	No CACP	Measured	2.5
EBCT studies in asymptomatic populations							
Arad[102]	1173	53	3.6	CACP >160	CACP <160	Self-reported	20.2
Detrano[104]	1196	66	3.4	CACP >44	CACP <44	Measured	2.3
Park[105] (subset of Detrano[104])	967	67	6.4	CACP >142.1	CACP <3.7	Measured	4.9
Raggi[107]	632	52	2.7	Top quartile†	Lowest quartile	Self-reported	1.3
Shemesh[112]	446	64	3.8	CACP >0	CACP = 0	Measured	2.8
Wong[110]	926	54	3.3	Top quartile	Lowest quartile	Self-reported	8.8
Arad[114]	4613	59	4.3	CACP ≥100	CACP <100	Measured	9.2
Kondos[111]	5635	51	3.1	CACP	No CACP	Self-reported	3.86 (men) 1.53‡ (women)
Greenland[1]	1312	66	7.0	CACP >300	No CACP	Measured	3.9
Shaw[112]	10377	53	5	CACP 401–1000	CACP ≤10	Self-reported	6.2§
Taylor[115]	2000	43	3	CACP	No CACP	Measured	11.8
LaMonte[117]	10746	54	3.5	CACP top third	No CACP	Measured	8.7 (men) 6.3 (women)
Vliegenthart[116]	1795	71	3.3	>1000	0–100	Measured	8.1
Becker[118]	924	60	3	Top quartile (75th percentile)	Total study group	Measured	7.3

Duplicate series: Detrano, Park, and Greenland.

CACP indicates coronary artery calcium score; RR, relative risk ratio.

*Using age- and gender-matched cohorts, representing top quartile.

†Using age- and gender-matched cohorts, representing the top quintile.

‡After multivariate analysis, $P < 0.05$ for men, $P =$ not significant for women.

§End point was all-cause mortality.

Tomography and expands the scope to both Multi-Detector Computed Tomography (MDCT) and covers other applications beyond calcium scoring, including computed tomography angiography (CTA). This statement reflects changes since the initial publication of these guidelines in 2000. The Writing Committee considered evidence published and drafted revised recommendations to incorporate results from major prospective outcome and diagnostic trials. This paper compared MDCT and EBCT, served as a clinical update for the use of CACP in clinical decision-making regarding evaluations for CHD in the asymptomatic individual, and summarized current comparative evidence regarding noninvasive angiography using computed tomography. The future role of these techniques was considered with regard to the monitoring of atherosclerosis and the detection of noncalcified plaque.

Table 20.2 Interpretation and Recommendations for CT Heart Scanning and CACP Scoring

1. A negative test (score = 0) makes the presence of atherosclerotic plaque, including unstable or vulnerable plaque, highly unlikely.
2. A negative test (score = 0) makes the presence of significant luminal obstructive disease highly unlikely (negative predictive power by EBCT on the order of 95% to 99%).
3. A negative test is consistent with a low risk (0.1% per year) of a cardiovascular event in the next 2 to 5 years.
4. A positive test (CAC >0) confirms the presence of a coronary atherosclerotic plaque.
5. The greater the amount of coronary calcium, the greater the atherosclerotic burden in men and women, irrespective of age.
6. The total amount of coronary calcium correlates best with the total amount of atherosclerotic plaque, although the true "atherosclerotic burden" is underestimated.
7. A high calcium score (an Agatston score >100) is consistent with a high risk of a cardiac event within the next 2 to 5 years (>2% annual risk).
8. Coronary artery calcium measurement can improve risk prediction in conventional intermediate-risk patients, and CACP scanning should be considered in individuals at intermediate risk for a coronary event (1.0% per year to 2.0% per year) for clinical decision-making with regard to refinement of risk assessment.
9. Decisions for further testing (such as stress testing or cardiac catheterization) beyond assistance in risk stratification in patients with a positive CACP score cannot be made on the basis of coronary calcium scores alone, as calcium score correlates poorly with stenosis severity in a given individual and should be based upon clinical history and other conventional clinical criteria

Adapted from ACC/AHA expert consensus document on EBCT for the diagnosis and prognosis of CAD.[4]

Coronary calcium scanning

The majority of published studies have reported that the total amount of coronary calcium (usually expressed as a score generated from the area and density of individual plaque measurements) predicts incident coronary disease events beyond that predicted by standard risk factors (see Table 20.1) expressed as a multifactorial risk index (the Framingham Risk Score, or FRS). The available evidence clearly shows that CACP is both independent and incremental to traditional risk factors with an up to 10-fold increase in predicted CHD event rates.

Summary from the AHA Scientific Statement

Table 20.2 outlines the recommendations for Calcium Scanning from the 2006 Scientific Statement.

Coronary calcium scanning

Class IIb

Coronary calcium scanning in intermediate CAD risk patients *(Level of Evidence B)* to refine risk prediction and select patients for altered targets of lipid-lowering therapies.

Coronary calcium assessment may be reasonable for the assessment of symptomatic patients, especially in the setting of equivocal treadmill or functional testing. *(Level of Evidence: B)*

Using calcium scanning to determining the etiology of cardiomyopathy. *(Level of Evidence B)*

Triage patients with chest pain patients with equivocal or normal electrocardiograms and negative cardiac enzyme studies. *(Level of Evidence B)*

Class III

Asymptomatic low risk (<10% 10-year risk) and high risk (>20% 10-year risk) Patients do not benefit from CAC measurement. *(Level of Evidence: B)*

It is not recommended to use CACP measure in asymptomatic persons to establish the presence of obstructive disease for subsequent revascularization. *(Level of Evidence: C)*

Serial imaging for assessment of progression of coronary calcification is not indicated at this time. *(Level of Evidence: B)*

Additional statements/guidelines related to coronary artery calcium

Other scientific statements also have endorsed the conceptual approach to refining the cardiovascular risk assessment through CACP detection. For example, the National Cholesterol Education Program (ATP III) stated that "In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denote advanced

coronary atherosclerosis and provide a rationale for intensified LDL-lowering therapy" [2]. A Clinical Expert Consensus Document of the American College of Cardiology published in 2007 [3], specified that coronary calcium measurements in clinically-selected intermediate CAD risk patients (e.g., those with a 10–20% Framingham 10-year risk score) was a reasonable option to refine clinical risk prediction and to select patients for altered targets for lipid-lowering therapies. Results from ongoing studies (listed below) should strengthen the recommendation, as the results of these trials were unavailable at the time of writing the current guidelines.

ACC/AHA Expert Consensus Document on coronary calcium

- The Committee judged that it was appropriate to consider use of CAC measurement in such [intermediate risk] patients based on available evidence that demonstrates incremental risk prediction information in this selected patient group. This conclusion is based on the possibility that such patients might be reclassified to a higher risk status based on high CAC score, and subsequent patient management may be modified.
- The Committee does not recommend use of CAC measurement in patients with low CHD risk (below 10% 10-year risk of estimated CHD events).
- The Committee does not advise CAC measurement in asymptomatic patients with high CHD risk (greater than 20% estimated 10-year risk of estimated CHD events, or established coronary disease, or other high-risk diagnoses). This selected patient stratum are already judged to be candidates for intensive risk reducing therapies based on current National Cholesterol Education Program guidelines.
- Current clinical practice guidelines indicate that patients classified as high risk based on high risk factor burden or existence of known high-risk disease states (e.g., diabetes) are regarded as candidates for intensive preventive therapies (medical treatments). There is no clear evidence that additional noninvasive testing in this patient population (high coronary calcium score e.g., CAC >400) will result in more appropriate selection of treatments.
- Evidence indicates that symptomatic patients considered to be at low risk of coronary disease by virtue of atypical cardiac symptoms may benefit from CAC testing to help in ruling out the presence of obstructive coronary disease. Other competing approaches are available, and most of these competing modalities have not been compared head-to-head with CAC.

Comparison with European Guidelines

The recommendations from the AHA and ACC are very similar to those of the European guidelines [4]. The European guidelines state, "The resulting calcium score is an important parameter to detect asymptomatic individuals at high risk for future CVD events, independent of the traditional risk factors." The guidelines state that calcium scanning should be used as a tool to improve risk assessment in individual patients. This organization further acknowledged that the prognostic relevance of CAC has been demonstrated in several prospective studies, not only in asymptomatic individuals but also in patients undergoing coronary angiography. However, screening for CAC should be reserved to individuals at intermediate risk and in men older than 45 years and women older than 55 years.

British Cardiovascular Society (BCS) Working Group recommendations for CT [5]. Currently, the role of MDCT in clinical practice is reserved for patients who following other noninvasive investigations remain a diagnostic problem, or where the angiogram has failed to identify proximal coronary anatomy, for example, failure to obtain detailed assessment of the coronary ostia or grafts.

In selected patients, the disadvantage of the radiation dose can be balanced by specific valuable information it provides. The number of patients likely to fulfill such criteria (confirmation of suspicion of CAD) is probably in the order of 10% of all those presenting to the cardiologist/cardiovascular physician.

Another area in which MDCT may play an increasing important role is in the diagnosis of patients presenting with acute chest pain. The "triple scan" in which pulmonary embolus, acute coronary syndromes and aortic dissection are excluded in a single examination performed in less than 10 minutes from start to finish is an exciting concept, and may well have a major impact on management in the future. Added to the ability to assess LV function, this technique may well become the first-line investigation in the future.

Cardiac CT Angiography – Scientific Statement 2006

CT angiography is rapidly becoming a standard tool in the outpatient evaluation of coronary artery disease. The improved resolution and number of detectors has made this test highly accurate compared to invasive angiography. In a meta-analysis comparing CTA to MRA [6], a comparison of sensitivity revealed higher diagnostic accuracy for MDCT (weighted [by the proportional sample size] average: 82%, 95% CI: 79–90%) when compared with MRA (weighted average: 75%, 95% CI: 60%–84%, $P = 0.029$).

A recent meta-analysis by Stein *et al.* [7] reported the average sensitivity and specificity values were 95% and 84% for 4-slice CT and noted a high diagnostic accuracy for both 16- and 64-slice CT. Diagnostic specificity values were 90% or higher for proximal, mid, and distal segments. These diagnostic values are very favorable compare to current noninvasive imaging techniques, such as nuclear or echocardiographic stress testing (Table 20.3).

For patients with a clinical suspicion of obstructive CAD, the high negative predictive value (>98% in most studies) may be useful to obviate the need for invasive coronary angiography in patients in whom symptoms or an abnormal stress test result require to rule out the presence of coronary artery stenoses. Especially if symptoms, age, and gender suggest a low to intermediate probability of hemodynamically relevant stenosis [8] ruling out hemodynamically relevant stenoses by CT coronary angiography may be clinically useful and may help avoid invasive angiography.

While utility of this tool for coronary anomalies and bypass grafts has been established, the utility of this tool to assess stent patency and assessment of noncalcific plaque still needs to be established. At the time of the AHA 2006 statement (Table 20.4), radiation exposure doses for cardiac CT were in the 10–18 mSev range (similar to nuclear imaging doses). New techniques to lower radiation dose and contrast requirements continue to be developed, and will be important in the future implementation of this tool in larger populations. Radiation dose reduction techniques (available since the AHA statement of 2006) include: dose modulation (lowers radiation dose 30–48%); reduction of kVp to 100 for thinner patients (lowers radiation dose by 40%), limit top and bottom of scan field (lowers radiation dose by 20%) and prospective triggering (lowers radiation dose by 70%). Use of all of these techniques results in CT angiograms with doses as low as 1 mSev (lower than coronary angiography).

Hybrid imaging with CT and nuclear imaging

Currently available and an area of ongoing clinical research is the application of hybrid PET-CT and SPECT-CT scanners. This will allow for the acquisition of metabolic and/or perfusion information as well as anatomic data including both coronary calcification as well as angiographic data. The incremental benefit of hybrid imaging strategies will need to be demonstrated prior to clinical implementation, as radiation exposure may be significant with dual nuclear/CT imaging. At this time there is no data supporting the use of hybrid scanning to assess cardiovascular risk or presence of obstructive disease.

Recommendations

CT angiography

Class IIa

CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients. *(Level of Evidence: B)*

Table 20.3 Sensitivity and specificity of diagnostic tests for evaluation of CAD

	No. of patients	Sensitivity (%)	Specificity (%)
Stress treadmill[85]	2456	52	71
Exercise SPECT[85,86]	4480	87	73
Stress echocardiography[85]	2637	85	77
EBCT calcium[22,23,89]	5730	85	75

Table 20.4 Radiation Doses With EBCT and MDCT Coronary Angiography

Author, year[Referens]	EBCT effective dose	MDCT prospective trigger	MDCT retrospective gating	EBCT angiography	MDCT angiography	Cardiac catheterization
Becker, 1999[45]	0.8 mSv		5.3 mSv			3.3 mSv
Ohnesorge, 2002[82]			3.0 mSv (m) 4.0 mSv (f)			
Cohnen, 2001[73]			2.8 mSv (m) 3.6 mSv (f)			
Jakobs, 2002[84]		2 mSv (m) 2.5 (f) 1 mSv (m)* 1.4 (f)*				
Hunold, 2003[10]	1 mSv (m) 1.3 mSv (f)	1.5 mSv (m) 1.8 mSv (f)	3 mSv (m) 3.6 mSv (f)	1.5 mSv (m) 2.0 mSv (f)	10.9 mSv (m) 13.0 mSv (f)	2.1 mSv (m) 2.5 mSv (f)
Morin, 2003[8]	0.7 mSv	1.0 mSv	2.6–4.1 mSv	1.1 mSv	9.3–11.3 mSv	
Kopp, 2002[169]			7.6 mSv (m) 9.2 mSv (f)			
Achenbach, 2001[166]			6.7 mSv (m) 8.1 mSv (f)			
Flohr, 2003[77]		0.5 mSv (m) 0.8 mSv (f)	1.9–2.2 mSv (m) 2.8–3.1 mSv (f) 1–1.5 mSv (m)* 1.4–2 (f)*		5.7–7.1 mSv (m) 8.5–10.5 mSv (f) 2.9–5 mSv (m)* 4.2–7.4 mSv (f)*	
Trabold, 2003[78]			2.9 mSv (m) 3.6 mSv (f) 1.6 mSv (m)* 2 mSv (f)*		8.1 mSv (m) 10.9 mSv (f) 4.3 (m)* 5.6 (f)*	
Carr, 2000[42]	0.6 mSv (m) 0.7 mSv (f)	0.9–1.5 mSv (m) 1.1–1.9 mSv (f)	4.6 mSv (m) 5.6 mSv (f)			
Raff, 2005[80]					13 mSv (m) 18 mSv (f)	

(m) indicates male; (f), female.

*With dose modulation.

CT coronary angiography is reasonable to use as one of the first choice imaging modalities in the evaluation of known or suspected coronary anomalies. *(Level of Evidence: C)*

Class IIb

It may be reasonable in most cases to not only assess the patency of bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site as well as in the native coronary artery system. *(Level of Evidence: C)*

Class III

Use of CT angiography in asymptomatic persons as a screening test for atherosclerosis (noncalcific plaque) is not recommended. *(Level of Evidence: C)*

CT coronary angiography to follow up stent patency cannot be recommended. *(Level of Evidence: C)*

CT coronary angiography to assess noncalcific plaque is not recommended, as there is no prognostic information to determine whether noncalcified plaque adds any information on top of risk factors, angiographic disease severity or calcified plaque. *(Level of Evidence: C)*

Hybrid scanning (nuclear and CT)

Class III

The incremental benefit of hybrid imaging strategies will need to be demonstrated prior to clinical implementation, as radiation exposure may be significant with dual nuclear/CT imaging. Therefore, hybrid nuclear/computed tomographic imaging is not recommended. *(Level of Evidence C)*

Ongoing trials

The results from the Multi-Ethnic Study of Atherosclerosis [9,10], demonstrates significant predictive power of coronary artery calcification in a multiethnic, population-based study. This study was not available at the time of the AHA statement or ACC/AHA joint statement on coronary calcium and adds considerable strength to the recommendation for use as a risk stratification tool. In a study of 6814 persons followed for over 3.5 years, the age, race/ethnicity, and sex-adjusted HRs (95% CI) for CAC scores to predict cardiovascular events of 0, 1–99, 100–399, and ≥400 were 1.0, 4.7 (95% CI 2.5–8.7), 11.5 (95% CI 6.2–21.5), and 16.1 (95% CI 8.5–30.8), respectively. This study found that CAC predicts subsequent CVD events better than does carotid intima-media thickness.

Another large population based study is the Heinz Nixdorf Recall Study [11], an ongoing study in 4800 men and women (47% female) that will assess the natural history after calcium scoring, as neither the physician nor the patient will be aware of the calcium scores. This study will also assess stress testing and its interplay with coronary calcium testing. The results of this study should be available in the next year.

Future directions

Tracking progression of subclinical atherosclerosis

A proposed use of CACP measurement is to track atherosclerotic changes over time using serial measurements. There are several published studies of outcomes related to CACP progression. The first study demonstrated, in 817 persons, that EBCT-measured progression was the strongest predictor of cardiac events [12,13]. This observational study suggests that continued accumulation of CACP in asymptomatic individuals is associated with increased risk of MI in asymptomatic individuals. A second study measured the change in CACP in 495 asymptomatic subjects submitted to sequential EBCT scanning. On average, MI subjects demonstrated an annual rate of CACP change of 42% ± 23%; event-free subjects showed a 17% ± 25% yearly change ($P = 0.0001$). The associated relative risk for acute MI for patients exhibiting ≥15% CACP progression was elevated 17.2-fold (95% CI: 4.1 to 71.2) when compared to those without CACP progression ($P < 0.0001$).

A large prospective study using EBCT to measure progression of CACP has been reported. This prospective observational study evaluated 4613 asymptomatic persons aged 50 to 70 years with EBCT scanning of the coronary arteries at baseline and again at 2 years and follow-up for 4.3 years [14]. This study demonstrated that the median (interquartile range) calcium score increased by 4 (0, 38) units from baseline to the year two scan in subjects who did not sustain a coronary event at any time during the study. In contrast, median (interquartile range) calcium scores increased by 247 (40, 471) units between the baseline and 2-year examinations in subjects who experienced a first coronary disease event after the year 2 scan ($P < 0.0001$). Multiple logistic regression demonstrated only age ($P = 0.03$), male gender ($P = 0.04$), LDL-cholesterol ($P = 0.01$), HDL-cholesterol ($P = 0.04$), and two-year change in calcium score ($P = 0.0001$) were significantly associated with subsequent CAD events. Increasing calcium scores were most strongly related to coronary events in this clinical study, similar to prior observational studies. Despite this information, it is difficult to justify the incremental population exposure to radiation and cost associated with a repeat CT test to assess "change" until it is better understood what therapies may be of benefit and how clinicians should utilize this data in clinical practice.

Several large observational studies, such as MESA (utilizing both EBCT and MDCT) [9,10] and RECALL (using EBCT) [11], are currently underway

to also assess the prognostic value of increasing CACP burden in population based samples. Genetic studies measuring calcified plaque with MDCT, such as NHLBI's Family Heart Study-SCAN are also ongoing and will utilize the vascular calcium phenotype as a means of identifying genes related to atherosclerosis and CVD.

Conclusions

The most promising use of cardiac CT at this time is calcium scoring for risk-assessment of the asymptomatic individual whereby elevated calcium scores may lead to more vigorous application of both lifestyle and/or pharmacologic therapies targeted to lower cardiovascular risk and CT angiography to rule out the presence of coronary stenoses in certain subsets of symptomatic patients.

2008 Statement on noninvasive coronary artery imaging: MR angiography and multi-detector CT angiography [15]

This statement provides a discussion of technical issues, applications, advantages, and limitations for both MRA and CTA, and recommendations for current and future uses.

Noninvasive coronary CTA and MRA represent substantial advances that may ultimately be very valuable for diagnosis of significant coronary artery disease. The chief advantages of coronary CTA compared to MRA are wider availability, higher spatial resolution, and more consistent, shorter examinations with better patient compliance. Coronary MRA has the advantages of lack of ionizing radiation and lack of administration of iodinated contrast material. Both tests are currently suboptimal in patients with atrial fibrillation and other arrhythmias, image quality may further be reduced by high body mass.

Specific recommendations for use of CTA and MRA

1 Neither coronary CTA nor MRA should be used to "screen" for coronary artery disease.

2 No multi-vendor trial data are available for MDCT coronary CTA or for current whole-heart coronary MRA. Thus, the ability of these methods to be widely applied other than at the reporting research centers is unknown. Both multi-vendor and additional multi-center validation of these methods needs to be performed before widespread acceptance in routine clinical practice.

3 The potential benefit of coronary angiography by CT or MR is likely to be greatest for symptomatic patients at intermediate risk for coronary artery disease after initial risk stratification, including patients with equivocal stress test results. Diagnostic accuracy favors coronary CTA over MRA for these patients. Concerns regarding radiation dose limit coronary CTA in risk patients with very low pre-test likelihood of coronary stenoses; patients with a high pre-test likelihood of coronary stenoses are likely to require intervention and require invasive catheter angiography for definitive evaluation. Pronounced coronary calcification may negatively impact interpretability and accuracy of coronary CTA.

4 Anomalous coronary artery evaluation can be performed by either CTA or MRA; radiation protection concerns indicate MRA is preferred when it is available.

5 Reporting of coronary CTA and MRA results should describe any limitations as to the technical quality of the examination and the size of the vessels, descriptions of coronary anomalies, coronary stenosis and significant noncardiac findings within the field of view.

6 Continued research in CT and MR techniques is encouraged to determine the potential of these noncatheter based modalities to detect, characterize and measure atherosclerotic plaque burden as well as its change over time or as the result of therapy.

ACCF/AHA 2007 clinical competence statement on vascular imaging with computed tomography and magnetic resonance [16]

This statement is the first American College of Cardiology/American Heart Association (ACC)/AHA document on clinical competence in vascular computed tomography (CT) and magnetic resonance imaging (MRI) and is designed to assist in the assessment of physicians' competence on a procedure-specific basis. The minimum experience, knowledge base, and technical skills necessary for the competent performance of vascular CT and MRI are specified.

Several applications were outlined, as described below.

CT angiography

Specific applications

Aorta

CTA allows diagnosis of thoracic aortic aneurysms and dissections, aortic dissection, aortic aneurysm (including monitoring its expansion over time), traumatic aneurysms of the thoracic aorta, sinus of Valsalva aneurysms, and coarctation of the aorta. CTA has utility in patients undergoing "redo" coronary artery bypass surgery. CTA may guide the surgical approach by defining the position of the sternum to the right ventricle, existing grafts, and aorta and thereby avoid unnecessary complications. The presence of severe aortic plaque raises the risk of stroke during "redo" surgery.

Upper extremity arteries

There is limited clinical data on the utility and performance of CTA for the diagnosis and management of upper extremity arterial disease. Subclavian artery stenosis from a number of diseases, including atherosclerosis and vasculitis, can be effectively diagnosed using CTA. CTA allows accurate measurements of the diameter of the area to be treated as well as the length of the appropriate endograft. CTA can also be utilized for post-intervention surveillance to assess for endoleaks or deformity of the device. Recognition of the etiology and anatomic location of the ischemic upper extremity, including atherosclerotic disease, embolism (cardiac and vascular sources including thoracic outlet syndrome), and vasculitis is possible by CT. CTA provides important information on the anatomy of the thoracic outlet. Hemodialysis access and shunt patency is commonly performed with CTA. Because there is no concern for exacerbating renal dysfunction with iodinated contrast administration in hemodialysis patients, CTA offers a rapid, high spatial resolution study to assess graft patency and arterial inflow and venous outflow.

Extracranial cerebrovascular arteries

CT is often the initial test in patients with transient ischemic attack (TIA) or stroke to exclude hemorrhage and to detect early changes associated with ischemia. CTA can be added to a CT examination, adding only 5 to 10 minutes to the study and providing real anatomic detail. 3D reconstructions of the carotid often permit a more complete assessment of eccentric lesions, including dissection. In regard to cerebral aneurysms, CTA can readily define their size, length, and diameter. CTA may demonstrate a small irregular lumen even when other studies such as magnetic resonance angiography (MRA) or carotid ultrasound suggest occlusion.

Pelvic and lower limb arteries

A complete acquisition of lower extremity inflow and run-off is presently available with MDCT angiography that was not previously available with fewer detectors. The increase in spatial resolution now afforded by CTA allows the differentiation between high and low-grade stenoses in peripheral vasculature, and the characterization of the nature of the lesion, differentiating atheromatous from thrombotic stenoses. CTA has been shown to have excellent correlation with DSA. CTA allows visualization of inflammatory and aneurysmal diseases, thromboembolic disease, vascular injury, spontaneous and iatrogenic dissections, and congenital abnormalities. The capacity of CTA to visualize the arterial wall, as well as the lumen, provides the interpreter a greater degree of certainty when arriving at less common diagnoses. The potential utility of CTA in the evaluation of graft patency is important as well as in the detection of graft-related complications (graft stenosis, aneurysmal changes, and arteriovenous fistulas). Practitioners of CTA should recognize The CTA provides value in the setting of peripheral vascular trauma in the assessment of complicated or partial occlusions, arteriovenous fistulae, intimal flaps, and pseudoaneurysms.

Renal arteries

CT angiography provides accurate assessment of the various etiologies of renal artery stenosis, including atherosclerosis, fibromuscular dysplasia, and other causes of renovascular disease such as polyarteritis nodosa, arteriovenous fistulae, aneurysms, thrombosis, and embolism. Identification of renal parenchymal enhancement patterns identifying the cortex, medulla, and the collecting system is important for the recognition of intrinsic parenchymal disease.

Mesenteric arteries
CTA allows assessment of the different etiologies and pathophysiology of mesenteric ischemia such as atherosclerosis, arterial thrombosis or embolism, vasculitis, celiac trunk compression from the median arcuate ligament, and mesenteric vein thrombosis.

CT venography
CTA is useful for demonstrating deep venous thrombosis (DVT), especially the proximal extent into the iliac vein or inferior vena cava (IVC). CT venography provides direct imaging of the IVC, pelvic and lower extremity veins immediately after CT of the pulmonary arteries without injection of additional contrast material, adding only a few minutes to the examination. A single examination capable of evaluating both the pulmonary arterial system and the pelvic and lower extremity venous system may offer advantages over other tests directed at either diagnosis alone. Adding CT venography to CTA increases the sensitivity for pulmonary embolism without reducing specificity. The use of CT venography in the evaluation of venous thrombosis involving the upper extremity veins (brachiocephalic and axillary veins) is important, especially in cases of suspected venous thrombosis due to malignancies (malignant superior vena cava syndrome). Owing to the superior discriminatory properties of CT for lung parenchyma over MRI, CT venography in conjunction with CT of the chest is the diagnostic study of choice for this type of evaluation.

Magnetic resonance angiography

Aorta
MRA is an excellent technique to define the overall size, shape, and extent of aortic aneurysms. MRI has excellent sensitivity and specificity for the determination of a presence of dissection, and it can cover large fields of view, permitting full assessment of its extent. It should be recognized that MRI offers certain advantages in aortic dissection, including the ability to characterize thrombus or slow flow in the false lumen by exploiting differences in signal properties.

Upper extremity arteries
Interpreters of MRA should understand that atherosclerosis is the cause of the majority of stenotic and aneurysmal disease in the arteries of the upper extremities and that MRA is quite accurate in its diagnostic capacity in this regard. Utility is to recognize "subclavian steal syndrome" and the ability to depict reversal of flow as well as the ability to depict the precise site of anatomic obstruction. Knowledge of the use of multiple MR techniques in the evaluation of inflammatory arteritis, Takayasu's arteritis, giant cell arteritis that can lead to stenoses or aneurysmal dilation in the thoracic aorta and subclavian and axillary arteries. MR can be useful in the diagnosis of thoracic outlet syndrome. MRA is an excellent test for evaluation of the arch.

Extracranial cerebrovascular arteries
As MRI is used frequently in stroke, MRA can be included with only a few minutes of added scan time. The intracranial carotid artery is easily demonstrated with MRA, and gadolinium-enhanced MRA allows imaging of the entire circulation from the aortic arch to the first division of the major intracranial arteries. The addition of cerebral MR perfusion contributes complementary information and together with MRA can improve understanding of the clinical significance of arterial lesions. Pitfalls of MRA, including the effects of movement, turbulence, and slow flow, should be considered.

Pelvic and lower limb arteries
Diagnosticians should be cognizant of techniques to reduce venous contamination.

Physicians should recognize the high sensitivity and specificity of MRA for the diagnosis of PAD and the utility of MRA for assessing graft patency, as well as inflow and outflow disease. MRA helps delineate aneurysms, presence of intramural clot, dissection, and atherosclerosis.

Renal arteries
Practitioners of MR should appreciate that renal artery stenosis is an important cause of secondary hypertension. Renal MRA allows evaluation of the renal arteries and accessory renal arteries directly, establish the site and severity of stenoses, and their hemodynamic significance, measure kidney size and parenchymal thickness, and identify perirenal and aortic pathology.

Mesenteric arteries
Physicians should recognize that unlike acute mesenteric ischemia, chronic mesenteric ischemia due to atherosclerotic disease is well-suited for evaluation by MRA. Knowledge of the appropriate pulse sequence to use for this disorder is essential. MRA can recognize anatomic variations and celiac artery pseudostenosis, and for examining the extent and nature of external compression on mesenteric arteries or veins.

MR venography
MR venography visualizes the major venous sinuses, allowing visualization of occlusive disease associated with infarction.

Whole body MRA
The clinical value of whole body MRA has not yet been systematically tested in large populations.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book these relevant AHA statements and guidelines were published: Safety of Magnetic Resonance Imaging in Patients With Cardiovascular Devices, http://circ.ahajournals.org/cgi/content/full/116/24/2878; Noninvasive Coronary Artery Imaging: Magnetic Resonance Angiography and Multidetector Computed Tomography Angiography, http://circ.ahajournals.org/cgi/content/full/118/5/586.

Appendix
Update on Coronary Artery Bypass Surgery: Current and Future Trends

Robert A. O'Rourke

CABG or PCI vs. OMT
CABG vs. PCI
Generalization
Observational studies
Specific subgroups
Lack of sufficient RCT data

CABG or PCI vs. OMT

Coronary artery bypass graft (CABG) surgery and catheter-based percutaneous coronary intervention (PCI), with or without coronary stents, are alternative approaches to mechanical coronary revascularization [1]. However, the comparative effectiveness of CABG and PCI remains poorly defined for patients in whom both procedures are technically feasible and myocardial revascularization is clinically indicated. Furthermore, the use of intensive optimal medical therapy (OMT) of chronic stable angina has never been proven to be inferior to revascularization except in patients who are at high risk for adverse cardiac events or who present with acute coronary syndromes [1–6]. In 1994 Yusuf and associates [7] performed a meta-analysis utilizing seven randomized clinical trials comparing coronary artery bypass graft surgery with an initial strategy of medical therapy to assess the effect on mortality in patients with stable coronary artery disease. These patients had stable angina with no necessity for initial surgery on grounds of symptoms alone or myocardial infarction.

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Patients ($n = 1234$) were assigned either for CABG surgery or the standard of care at the time ($n = 1325$) "meager management" considered suboptimal to current standards (see Table A.1). Anti-angina drugs such as beta-blockers, calcium blockers, ACE inhibitors, and effective long-acting nitrates were generally not available. Nevertheless, the proportion of patients in the medical group who had undergone CABG surgery was 25% in 5 years, 33% in 7 years, and 41% in 10 years; 93.7% of patients assigned top the surgical group underwent CABG surgery. The CABG group had significantly lower mortality than the medical group at 5 years (10.2 vs. 15.8, $P = 0.001$) and at 10 years (26.4 vs. 30.5%, $P = 0.03$). The risk reduction was greater in patients with left main coronary artery disease than in those with disease in three vessels. PCI has never been shown to be superior to CABG surgery for treatment of symptomatic stable coronary disease.

CABG vs. PCI

In patients with left main or triple-vessel coronary artery disease and reduced left ventricular function, CABG is generally preferred because randomized, controlled trials (RCTs) have shown that it improves survival compared with medical therapy. The use of intensive medical therapy for patients with stable angina has never been shown to be inferior to OMT in reducing recurrent myocardial infarction or cardiac death.

Recently, Bravata and associates [8] sought to evaluate the evidence from RCTs on the comparative effectiveness of PCI and CABG. They included trials using balloon angioplasty or coronary stents because quantitative reviews have shown no

Table A.1 A Meta Analysis Using 7 Randomized Trials of CABG Surgery vesus Medicine Treated Patients in 10 Years of Follow-Up

	5 years	7 years	10 years
Mortality in initially randomized to surgery	10.2%*	15.8%+	26.4%++
Mortality in initially randomized to medicine	15.8%*	21.7%+	30.5%++
Crossover from medicine to surgery	25%*	33%+	41%++

* + ++ All changes statistically significant. $N = 2{,}629$ patients. Adapted from Yusef S, Zucker D, Peduzzi P, *et al.*, Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet. 1994;344:563–570.

differences in mortality or myocardial infarction between these PCI techniques.

Generalization

Although the earlier trials of PCI vs. CABG continue to provide pertinent information about the "hard outcomes" of greatest importance after coronary revascularization, the perennial question about all randomized studies is whether the results can be generalized to less selected patient populations and practice settings. The randomized trials of PCI and CABG, as well as optimal medical trials, enrolled few patients who were older than 75 years of age, had depressed left ventricular function, heart failure, clinical instability, or had undergone previous CABG or PCI procedures. The results of the randomized trials do not necessarily apply to those other populations who were not well-represented due to the small number randomized [9].

Observational studies

The finding of similar long-term survival after randomization to PCI or CABG differs from the findings of studies based on several large clinical registries, which have reported improved survival after CABG. These large clinical registry studies were observational, nonrandomized comparisons, which are inherently less reliable than randomized trials because selection biases may be present that even statistical adjustment techniques cannot correct.

Specific subgroups

The incidence of specific clinical subgroups often reported is too small to make reliable conclusions about most clinical characteristics of interest. The most extensive evidence of high risk applies to patients with diabetes and those with triple-vessel coronary artery disease vs. double-vessel disease [8].

The adverse prognostic effect of diabetes has been reported consistently in patients undergoing coronary revascularization procedures and may be due to more extensive coronary disease at the time of revascularization, more rapid progression of coronary atherosclerosis during follow-up, or both factors.

Four randomized trials reported a larger difference in survival between CABG and PCI in patients with triple-vessel disease than in patients with double-vessel disease. Although this evidence is inconclusive, it is also suggested by the strong and statistically significant effect of the extent of coronary disease on the relative hazard after PCI or CABG reported by the Duke database and other large clinical registries [9–11]. This hypothesis could be tested by pooling individual patient-level data from randomized trials of PCI and CABG conducted in patients with multivessel disease.

Clinical trials are also needed to assess whether the availability of drug-eluting stents has affected the comparative efficacy of PCI and CABG.

In the last 30 years, life expectancy in the United States increased by 6.0 years [12]. Nearly two-thirds of this increase (3.9 years) is credited to reductions in mortality from cardiovascular disease and stroke, and approximately 7% of the improved cardiovascular survival benefit has been attributed to myocardial revascularization [13].

After the introduction of coronary artery bypass grafting (CABG) in 1967, revascularization trials from the United States and Europe showed improved survival with this technique in selected subgroups of high-risk patients (e.g. proximal left main coronary

artery disease) compared with the medical therapy available in that era [2]. However, the relatively high morbidity and mortality rate associated with CABG led to the development of PCI in the 1977. Techniques of PCI have evolved to include coronary artery stenting with bare-metal stents and, more recently, drug-eluting stents. The use of PCI to treat multivessel CAD rather than only single-vessel disease led to several RCTs comparing PCI and CABG [7].

The major results of a recent meta-analysis by Brevata [8] reveal that early procedural mortality rates (1.15% vs. 1.8%) and 5-year survival rates (89.7% vs. 90.7%) are no different after PCI and CABG. Brevata's meta-analysis has been seriously discredited by (1) the inclusion of the AWESOME trial [14]; (2) inclusion criteria which were exclusion criteria for other trials; and (3) inclusion of the ERACI II trial [15] which had a 5.6% mortality and finally the extent of the Stent or Surgery trial [16]. The latter favored CABG over PCI, but the trial was terminated after 2 years because of lack of funding. Also, the 5-year survival was similar after PCI and CABG in patients with and those without diabetes in the seven RCTs that reported on this subgroup. Compared with PCI, CABG provided more complete relief of angina in 5% to 10% of patients over 5 years, and repeated revascularization was less common. However, more procedural strokes occurred with the use of CABG than with PCI. Large observational registries indicate that patients with triple-vessel disease are much more likely to undergo CABG. Patients with single vessel disease are more likely to undergo PCI.

A post hoc analysis of the BARI (Bypass Angioplasty Revascularization Investigation) trial [17] suggests that a diabetic subgroup of patients have a longer post-procedure survival following CABG than primary PCI. This is being tested prospectively in the current BARI-2D study. Bravata and colleagues acknowledge the limitations of their meta-analysis, which merely reflect limitations in the entry criteria, sample size, outcome assessment, and reporting of available trials. For example, they could not analyze procedural myocardial infarction because of variable diagnostic criteria. Current techniques and devices, including drug-eluting stents, were not evaluated, and few patients older than 75 years or with poor left ventricular function, clinical instability, or previous revascularization were included in the trial.

The findings of Bravata and colleagues [8] cannot be generalized to all patients with coronary artery disease, but are most applicable to patients with intermediate disease severity, who constituted most participants. The short-term and long-term mortality rates associated with stable anti-ischemic therapy including PCI and CABG, are similar in these patients in discussing revascularization options with their patients; physicians should make this equivalence clear, because patients often have preconceived notions that one procedure or the other is superior. The advantages of CABG are better relief of angina and a lower likelihood of subsequent revascularization; however, the magnitude of the latter benefit may decrease in future randomized trials that include drug-eluting stents. The increase in stroke with CABG offsets these advantages. Physicians must ensure that their patients understand these differences. Another major factor is the cost effectiveness of the three major strategies. New quality of life data from the COURAGE trial will be published shortly.

For many patients, however, the most important question is whether neither PCI nor CABG is warranted. Until recently, recommendations for PCI or CABG in patients other than those in the highest risk group were based on observational data and consensus opinion [2].

Newer studies have challenged the frequently held assumptions that revascularization with CABG or PCI consistently reduces cardiac events and prolongs survival [18]. The recently published COURAGE trial indicates that patients with moderate to severe angina pectoris do not benefit from primary PCI strategy compared with OMT in relation to primary endpoints of death or myocardial infarction when compared to PCI alone. The OAT (Occluded Artery Trial) enrolled 2166 patients who had an occluded infarct-related coronary artery early after myocardial infarction and another high-risk criterion, such as proximal stenosis in a different coronary artery [18]. In OAT, PCI did not confer an advantage over medical therapy for the combined end-point of death, reinfarction, or New York Heart Association class IV heart failure.

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)

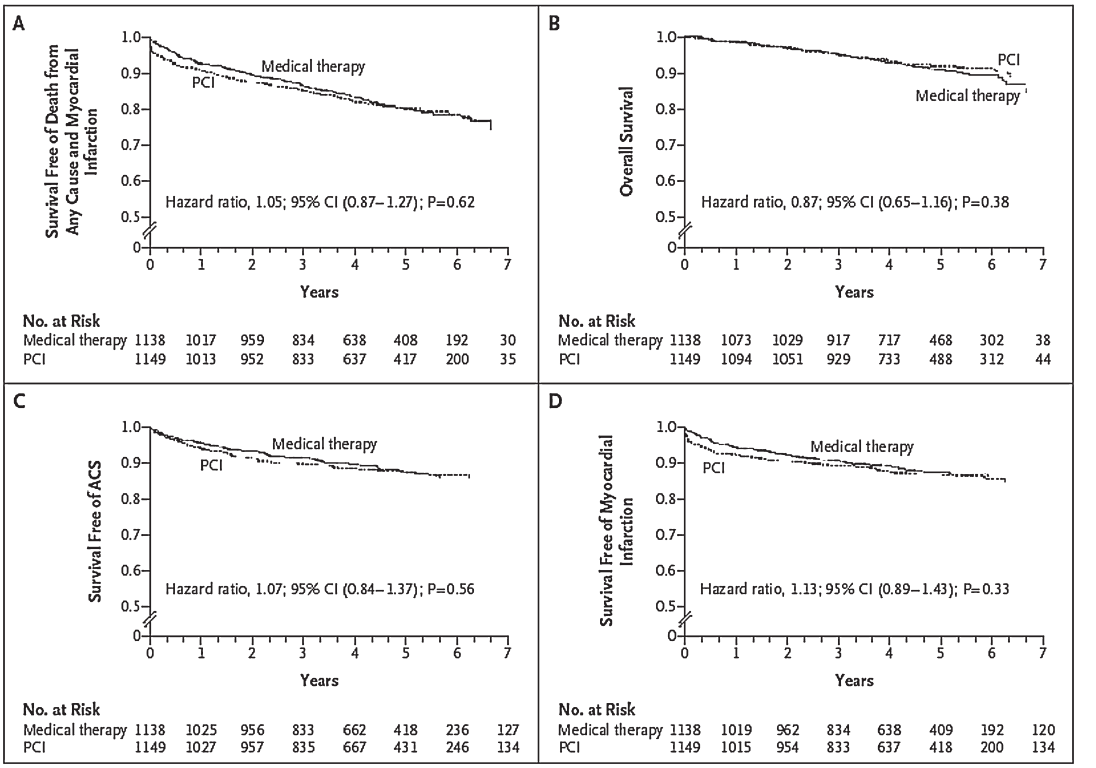

Fig. A.1 Kaplan-Meier COURAGE Trial survival curves.
In A, the estimated 4.6-year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0% in the PCI group and 18.5% in the medical-therapy group. In B, the estimated 4.6-year rate of death from any cause was 7.6% in the PCI group and 8.3% in the medical-therapy group. In C, the estimated 4.6-year rate of hospitalization for acute coronary syndrome (ACS) was 12.4% in the PCI group and 11.8% in the medical-therapy group. In D, the estimated 4.6-year rate of acute myocardial infarction was 13.2% in the PCI group and 12.3% in the medical-therapy group. From Passamani *et al.*, A randomized trial of coronary bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med. 1985;312:1665–1671.

trial [2], the largest reported RCT in chronic coronary artery disease, enrolled 2287 patients with significant coronary artery disease and inducible ischemia; 70% had multivessel disease, and more than one third had stenoses in the proximal left anterior descending artery [2] (see Figure A.1). The trial compared optimal medical therapy with and without PCI. Unlike medical therapy in earlier trials that focused on antianginal medication, all patients in the COURAGE trial received intensive, goal-directed risk factor reduction therapy that resulted in very high rates of adherence to guideline recommendations for blood pressure, lipid levels, exercise, diet, and smoking cessation [2]. When added to such intensive medical therapy, PCI had no advantage in terms of the primary end point of death or myocardial infarction and only a modest advantage in relief of angina that decreased over time. These results suggest that revascularization can safely be deferred for many patients if the standards for medical therapy in the COURAGE trial are strictly followed.

Lack of sufficient RCT data

Bravata and colleagues' review raises several concerns. The 23 RCTs meta-analysis included 9963 patients and spanned 40 years; however, in 2005 alone, more than 900,000 revascularization procedures were performed in the United States [2]. The number of these procedures performed on

patients like those in the trials is unknown, but the relatively small number of patients in RCTs is worrisome. In comparison, approximately 1,200,000 myocardial infarctions occur in the United States annually [2]. More problematic still is that only three of the RCTs were performed in the United States. These initiatives require much greater funding to conduct the necessary RCTs, as well as a greater commitment from U.S. patients and physicians to increase enrollment in future RCTs.

In this era of higher risk patients referred for cardiac surgery, avoidance of the use of a pump and the subsequent adverse systemic reaction has been regarded as a strategy to manage the risk of perioperative mortality and morbidity in coronary revascularization. With the increased age of the population and the increasing number of referrals for operation in patients with severe valvular disease (e.g. aortic stenosis) and diffuse calcified coronary artery stenosis, a changing strategy is necessary to manage the risk of perioperative mortality and morbidity in coronary revascularization and valvular heart disease. Many surgical referrals will be requested for patients with high risk morbidity and mortality.

However, the applicability of minimally invasive or off-pump coronary artery bypass grafting is limited by its technical profile and by the possibility of inadequate revascularization in some patients with severe stenosis and complex anatomy of the coronary lesions. An investigation by Mazzei and associates [19] provides evidence that the degree of the systemic inflammatory reaction and the release of markers of end-organ damage are comparably modest whether coronary revascularization is performed off-pump or on-pump with the use of the minimal extracorporeal circulation system. This biochemical finding is demonstrated by the comparability of mortality, morbidity, and intensive care unit/hospital length of stay after the use of either strategy despite a similar preoperative risk profile of the study groups.

Three questions must be answered. Should the minimal extracorporeal circulation system and off-pump coronary artery bypass grafting be considered equivalent tools to obtain a lower rate of perioperative morbidity? If so, should we more commonly use the minimal extracorporeal circulation system to perform on-pump coronary surgery in elderly and high-risk candidates? Will this approach facilitate complete revascularization and perhaps better graft patency rates than with off-pump coronary artery bypass grafting? Important answers to these queries cannot be obtained without rigorous multicenter investigations.

Despite initial promising results it is doubtful that improvements in CPB will ever achieve the results obtained by complete avoidance of CPB. Off-pump bypass can only deliver optimal results to patients if complete and precise revascularization is achieved. The learning curve for this new operation is longer than for the conventional arrested-heart procedure and requires a modified set of skills and techniques. There is considerable enthusiasm for the hypothesis that complete revascularization with multiple arterial grafts can occur without CPB and without aortic manipulation. Only time will tell.

References available online at www.Wiley.com/go/AHAGuidelineHandbook.

During the production of this book this relevant AHA statement and guideline was published: Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder, http://circ.ahajournals.org/cgi/content/full/117/18/2407.

Other Statements Published in 2008

The American Heart Association continually publishes statements and guidelines throughout the year. During the production of this book, the following statements and guidelines were published. The web site of this book, www.Wiley.com/go/AHAGuidelineHandbook, has links to these documents and others that have been published recently.

ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 Appropriateness Criteria for Stress Echocardiography
http://circ.ahajournals.org/cgi/content/full/117/11/1478

Hyperglycemia and Acute Coronary Syndrome
http://circ.ahajournals.org/cgi/content/full/117/12/1610

Management of Cocaine-Associated Chest Pain and Myocardial Infarction
http://circ.ahajournals.org/cgi/content/full/117/14/1897

Implementation and Integration of Prehospital ECGs into Systems of Care for Acute Coronary Syndromes
http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.190402

The Impact of Prevention on Reducing the Burden of Cardiovascular Disease
http://circ.ahajournals.org/cgi/content/full/118/5/576
(is an advocacy paper with ADA)

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Percutaneous and Minimally Invasive Valve Procedures
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http://circ.ahajournals.org/cgi/content/full/118/4/428

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Call to Action on Use and Reimbursement for Home Blood Pressure Monitoring
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Index

A-actin 238
A-actinin-2 240
A-cardiac actin 240
A-myosin 238, 240
A-tropomyosin 238, 240
Abciximab 35, 37, 57, 64, 130
ABI 166–8, 170–1, 174, 176, 182–3
Ablation 246, 253–4, 256, 260–9, 275, 285, 289
  asymptomatic PVC 275
  catheter 74, 281
  purkinje fiber potential 275
  RF 262
Abscess 282, 309–10, 313–7, 325, 330
ABSOLUTE trial 186
ACCORD 116
Accuracy, diagnostic 340, 343
ACE 33–4, 43, 64, 67–8, 70, 87, 168, 174–6, 218, 235
  inhibitor, *see* ACEI
ACEI 109–11, 114–5, 139, 175, 204, 206–13, 220, 227–34
Acetaminophen 78, 85
ACS 28, 31–3, 37, 39, 45, 145, 159, 188, 271
ACTION 103
Acute Catheterization and Urgent Intervention Triage Strategy 30, 31, 45
Acute coronary syndromes. *See* ACS
Acute respiratory distress syndrome 142
Adenoma 212
Adenosine 75, 82–3, 256–60, 263–4, 266, 268–9
Adriamycin 241
Adult Treatment Panel III. *See* ATP III
Advanced cardiac life support 50–1
Advanced Cardiac Life Support Subcommittee 271
AF 66, 68, 74, 80, 137, 140, 142, 158, 163, 229, 231–2, 234, 244–54, 255, 257–9, 263–9, 275, 285, 302–7, 311, 343
  Copenhagen 247–8
  lone 246, 249, 253
  nonvalvular 247–8
  paroxysmal 246, 253
  persistent 245, 251–2
  pharmacological cardioversion 249–50
  rate control, pharmacological 244
  recurrent 251, 253
AFASAK 247–8
Agonists, alpha-2 152, 161–2
Ajmaline 276, 290
Albuminuria 202, 210
Aldosterone antagonist 208–9, 212, 230, 233–5
Aldosterone blocker 227
Aldosterone, system 64, 68
Aldosteronism 202
Amaurosis 53
Ambulatory blood pressure 201
American Academy of Pediatrics 332
American Dental Association 332
American Diabetes Association 210
Aminophylline 259
Amiodarone 72–4, 232, 245–6, 249–50, 265–9, 276–81, 284–6, 290
Amiodarone Trial Meta Analysis 281
Amiodarone versus Inplantable Cardioverter-Defibrillator 276–81, 284–6, 290
Amoxicillin 333
Amyloidosis 241
Analgesia/anxiolytics 67
Anatomy, coronary 149
Andersen syndrome 239
Anesthesia 72–5, 162
Aneurysm 186, 344–5
  abdominal aortic 205, 215, 217, 219–20
  mycotic 314
  ventricular 71
Angina 4, 5, 14, 17, 29, 31, 32, 37, 41, 53, 61, 66–7, 72–3, 80–2, 134, 136–7, 139, 144–51, 155, 160, 162, 168, 178, 188, 202, 208–9, 225, 232, 250
  atypical 5
  chronic stable. *See* CSA
  stable 8, 13, 22
  unstable. *See* UA
  vasospastic 19

The AHA Guidelines and Scientific Statements Handbook
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Angiography 25, 31, 33–8, 40, 45, 57, 70, 72, 78, 81, 172, 277
aortic root 299–300
contrast 165, 172–3
coronary 274, 297–301, 306
CT. *See* CTA
diagnostic 34–5, 37
digital subtraction 173
magnetic resonance 172, 182–3
radionuclide 39, 274, 299
Angioplasty 146, 188
balloon 159–60
percutaneous transluminal coronary 136, 143
Angiotensin receptor blocker. *See* ARB
Angiotensin-converting enzyme. *See* ACE
Ankle-brachial index. *See* ABI
Ankyrin 239
Annuloplasty 308
Anorexia 283
Antagonist 17, 246–7, 249
nondihydropyridine calcium channel 245–6, 250
Anthracycline 240, 291
Antiarrhythmics versus Implantable Defibrillators 273, 278
Antibiotics 241
B-lactam 321
prophylactic 332, 334
Antibody, anti-digitalis 290
Anticoagulation 25–6, 28, 34–8, 42, 45, 57, 62–3, 68, 75, 78–9, 86, 89, 110, 113–4, 137, 209, 232, 246–9, 252, 302, 304, 310–1
Antiplatelet 25, 34–7, 41, 45–7, 57, 63–4, 68, 78, 86, 89, 110, 208–9, 232
Antipsychotics 290
Anxiety 67, 85, 87
Aorta 293, 300–2, 344
Aortic
stenosis. *See* AS
valve replacement. *See* AVR
Apnea, sleep 193, 202
Apolipoprotein 192, 194
Aprotinin 140–1
ARB 64, 68, 114–5, 204, 206–12, 213, 218, 228–31, 233–5
Arrest, cardiac 50, 73, 275–92
Arrhythmia 17, 35, 46, 60–1, 66, 72–4, 80–1, 83, 150, 255–6, 258–63, 266–7, 269, 274
CABG 134
cardiac 269
control 267
diagnoses 269
drug-induced electrophysiological 271
exercise-induced 256, 273–4, 30
genetic 286–7
life-threatening 274, 282–3, 288
mechanism 256
pathway-mediated 264
postoperative 140
risk 273
supraventricular 255–69
transient 270, 274, 283
VT, 149–50, 232 270–98
catecholaminergic polymorphic 287
Arsenic 240
trioxide 290
Arteriography 78, 83, 173, 225
Arteritis 345
Artery
brachial 201
circumflex 146–9
coronary 336, 342
iliac 168, 179–80
intracranial carotid 345
mesenteric 346
radial 145
renal 344
Arthritis, rheumatoid 241
ARVC 242, 284–5
ARVC/D 238–9
AS 294–8, 302
Aspirin (ASA) 26, 28–9, 33, 34–5, 38, 41, 42, 45, 50–1, 54–5, 63, 66, 68, 78, 80–1, 84–6, 89, 110–1, 113–4, 130, 140–1, 160, 175, 186, 216–7, 220, 247–9, 254, 305
Assessment
cardiac 291
carotid intima-media thickness 45
hemodynamic 69, 302, 304
individualized 105–6
LV function 297, 299–300
preoperative 161, 163
Asthma 33, 34, 55
Asystole 290
Ataxia, Friedreich's 238, 241
Atenolol 227, 268
Atherectomy 129, 179
Atheroembolism 173, 182–3
Atherosclerosis 129, 165–8, 171, 175, 179, 181, 188, 194, 336–7, 339, 341–5
Atorvastatin 190
ATP III 187, 189–93
Atrial
fibrillation. *See* AF
tachycardia 257–8, 263–4
Atrioventricular blocking agents. *See* AV
Atrioventricular nodal reciprocating tachycardia. *See* AVNRT

Atrophy, peroneal muscular 285
Atropine 75, 77–8, 259
Auscultation 167
Autosomal recessive disease 238–9
AV
  blocker 255, 257–8, 261, 263, 267–8, 282, 285, 290
  conduction 285, 291
  synchrony 71
AVNRT 255–7, 260–2
AVR 144, 297–302, 310
AVRT 256–8, 264
Azimilide 263
Azithromycin 335

B-type natriuretic peptide 226
Bacilli, aerobic gram-negative 329
Bacteremia 332–4
  persistent 309–10
  staphylococcal 309
Ballooning, apical 242
Baroreflex 274
Barth syndrome 241
Bartonella 328
Basic life support 104
Benazepril 227
Bepridil 290
Beriberi 241
Beta-myosin 238
Betaxolol 227
Beta blocker
    oral 209
    vasodilating 213
Beta-adrenergic blocker 192, 231
Bilevel positive airway pressure 66
Biomarkers 53–4, 276, 291
  cardiac 139, 276
  serial 53
  release of, after acute MI 26
Bioprosthesis 310–1
Biopsy, endomyocardial 225–6
Bisoprolol 206, 209, 227
Bivalirudin 26, 34–5, 37, 45, 63, 117, 127, 131–2
Bleeding, gastrointestinal 35, 216
Block, atrioventricular 272
Blockade
  aldosterone 70, 111, 114–5, 220
  beta-adrenergic 74–5
  beta-adrenoceptor 73
  nodal 291
  sequential nephron 228
Blocker-related toxicity 291
Blood pressure. *See* BP
BMI 202–3, 217–8, 225
Body mass index. *See* BMI
Boston Area Anticoagulation Trial for Atrial Fibrillation 247
BP 167, 174–6, 193, 216–7, 219
  abnormal exercise 285
  ambulatory 201
  control 200–2, 204, 206, 209–10
  and CVD 199
  goal 200, 202, 207–8
  levels 197–8
  lowering 200, 206, 209, 212–3
  treatment 196–213
Brachytherapy 132
Brachytherapy, vascular, versus repeat balloon expansion 129
Bradyarrhythmia 75, 78, 208, 275
Bradycardia 17, 34, 54, 67, 71, 73, 75, 77, 160, 163, 204, 247, 262, 277, 282
Brugada syndrome 239, 287, 291
Bruits 167, 202
Buerger's disease 169
Bumetanide 70, 228
Bupropion 141, 175
Butilide 267
Bypass
  aortobifemoral 179–80, 183
  axillofemoral-femoral 179–80, 183
  distal 185
  femoral-femoral 180, 183
  femoral-popliteal 172
  femoral-tibial 170, 172, 180, 185
  femoropopliteal-tibial 185
  graft 181, 184–5
  iliofemoral 180, 183
  lower extremity 181, 185
  operative 181
  surgery
    aortocoronary 120
    coronary 128
  surgical 172, 177
Bypass Angioplasty Revascularization Investigation 143, 145

CABG 39, 40–1, 52–3, 59–61, 63, 68–71, 73, 78–81, 92, 104, 121–4, 135–51, 216, 297–8, 300, 308
  concomitant 144
  cost efficiency of 134, 146
  emergency 126, 138, 149
  ischemic mitral regurgitation 308
  mortality 135, 149
  vs. PCI 347–8
  prior 150–1
  vs. PTCA 135

reoperative 140, 144, 151
surgery 141, 145
CAC 336–43
CACNA1C 239
CACNP 340–2
CACP 336–8, 342–3
CAD 13, 153–5, 160–1, 163, 204–5, 208, 215–6, 225–6, 231–2, 258–9, 261, 279, 297, 299, 306, 336, 338–40, 343
Calcification 297, 343
coronary 336, 338–40, 342
Calcium 17, 225, 282–3
channel blockers. *See* CCBs
scanning 338–9
scores 336–9, 342–3
Canadian Amiodarone Myocardial Infarction Arrhythmia Trial 281
Canadian Atrial Fibrillation Anticoagulation 247
Canadian Implantable Defibrillator Study 273, 278
Candesartan 64, 68, 209
Capacity, functional 155, 158
Captopril 227
Carbohydrates 189, 193
Cardiac Arrest Study Hamburg 273, 278
Cardiac Pacemakers and Antiarrhythmia Devices 282
Cardiac rehabilitation 91–107
Cardiac Rehabilitation/Secondary Prevention. *See* CR/SP
Cardiomyopathy 17, 158, 230, 236–43, 282, 284–5, 288–9, 291, 338
defined 236
hypertrophic 284–5, 291
infiltrative 282
ischemic 292
primary 237, 241
restrictive 241–2
RV 274, 284
secondary 237, 241
tachycardia-induced 253, 275
tachycardia-mediated 246
Cardiomyopathy Trial 279
Cardioplegia, blood 138–9
Cardiopulmonary
bypass 136
resuscitation 50, 276
Cardiovascular disease. *See* CVD
Cardioversion 245, 249, 251–2, 258–9, 265–8, 270, 276–7, 289, 291
electrical 246, 251
pharmacological 249
synchronized 75
Cardioverter-defibrillator, implantable 230
Carnitine 240–1
Carotene, beta 216, 220
Carteolol 227
Carvajal syndrome 239
Carvedilol 206, 209, 227
CASHD 136–7, 142–4, 150–1
Catecholaminergic polymorphic ventricular tachycardia. *See* CPVT
Catecholamine 260
Categories, Rutherford 181
Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation 254
Catheter 162–3, 331
Catheterization 52, 72, 78–9, 81–3
cardiac 52, 68, 297–303, 306, 338, 341
Caveolin 241
CCBs 33, 43, 64–5, 70, 204, 206–8, 212–3, 229, 261–3, 265, 276, 288
dihydropyridine 204
nondihydropyridine 33–4, 140
CD 143, 154–6, 158, 160–1, 197–200, 210–2
Cell junction disease 239
Cerebrovascular accident 138
Chagas disease 240–1
Channelopathies 236
CHD 117, 187–92, 194–5, 206, 212–3, 221, 239, 273–5, 288, 294, 334
unrepaired cyanotic 294
CHF 58, 61, 81, 83, 322, 326, 328, 331
Chlorothiazide 228
Chlorpromazine 290
Chlorthalidone 228
Cholesterol 43–4, 67, 109, 141, 173, 187–9, 191–2, 194–5
Cholestyramine 190
Chronic kidney disease. *See* CKD
Chronic obstructive pulmonary disease 143
Cilostazol 177–8
Cisapride 290
CK-MB 32, 118, 139
CKD 44, 48, 196, 200, 202, 204, 210–1
defined 211
ALLHAT 208
Clarithromycin 290, 335
Claudication 166–8, 170–2, 174–80
Exercise vs. Endoluminal Revascularization 186
intermittent 168, 176, 178–80
symptoms 168, 171, 175–6, 178, 180–1
Critical limb ischemia (CLI) 168–9, 181–3, 185
Clindamycin 335
Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial 132, 349–50
Clofibrate 190
Clonidine 204, 210
Clopidogrel 26, 28, 34–8, 41–2, 45, 63, 68, 81, 84, 86, 89, 109–10, 114, 130, 141, 145, 216, 220, 248–9

Clot, intramural 345
Coagulation 150
Cocaine 241
Colchicine 78
Colesevelam 190
Colestipol 190
Collagen disorders 240
Collapse, hemodynamic 71–2
COMMIT Study 26
Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease 312, 332
Compression, celiac trunk 345
Compromise, hemodynamic 58, 71, 73–4, 150, 276–7
Computed tomography angiography. *See* CTA
Conduction 240, 275
  antegrade 258, 263
Congenital heart disease. *See* CHD
Congestion, pulmonary 54, 64, 70
Congestive heart failure. *See* HF
Continuous positive airway pressure 66
Coronary
  artery noncalcified plaque 336–7, 342
  atherosclerotic heart disease. *See* CASH-D
  heart disease. *See* CHD
Cororary artery bypass graft. *See* CABG
Coronary Artery Bypass Graft Patch Trial 279
Coronary artery calcified plaque. *See* CACP
Coronary artery calcium 336–43
Corticosteroids 78, 189, 192
Councils on Clinical Cardiology and Epidemiology 196, 203, 271
Counterpulsation, intra-aortic balloon 69–70 69, 72
COURAGE Trial 132, 349–50
COX-2 34, 54, 85
Coxsackie 241
CPR 50, 276
CPVT 239–40, 287
CRD 205, 215, 217, 219–20
Creatine kinase-MB. *See* CK-MB
Creatinine 63, 68, 70, 202, 207
  clearance 26, 42, 44, 63, 132, 317
  serum 210, 225
CR/SP 91–2, 100, 104
  defined 92
  performance measurement sets 102, 104–7
Cryoablation 263
Cryoprecipitate 57
CSA 5, 9, 32, 92, 104, 208, 228, 232
CTA 25, 32–3, 37, 39–40, 44–5, 54, 172–3, 182–3, 274, 300, 302, 336–54
  coronary 343
  mesenteric artery 345
  renal artery 344
Cultures, blood 314–5, 321, 323, 331–2
CVD 91, 154, 158, 187–9, 193–5, 197–8, 211, 214–22
Cyclooxygenase (COX)-2-selective agents. *See* COX-2
Cyclophosphamide 241
Cyclosporine 190

DASH diet 203, 211–2
Daunorubicin 240–1
DBP 197–200, 204–5
DCM 236–7, 240–2
  nonischemic 284
Death 164, 167, 175, 214–5, 221–2, 238, 240, 242
  cardiac 150, 230, 238–40, 270
    275–98 291
    sudden 270–92
  cardiovascular 163, 236
  nonarrhythmic 281
  vascular 175
Defibrillation 50, 66
Defibrillator in Acute Myocardial Infarction Trial 279–80
Defibrillators 276, 289, 291–2
Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation 279
Dehiscence
  partial 313–4
  valvular 316, 325
Denervation, sympathetic neural 287
Depression, emotional 29, 44, 85, 87, 101, 106, 214, 221
Depression, ST-segment 27, 39, 45, 56, 60, 126, 274
Dermatomyositis 241
DES 26, 109, 111, 117, 130, 132, 146, 151, 159, 164, 349
Desmin 241
Desmoglein 239
Desmoplakin 239
DHA 218
Diabetes mellitus. *See* DM
Diabetic nephropathy 227
Diagnosis 165, 171, 174, 182
  etiologic 329
Dialysis 290
Diastolic blood pressure. *See* DBP
Diet 67, 203, 211–2, 214–5, 218, 226, 270, 283
  cholesterol-lowering 189. *See also* Nutritional counseling
Digitalis 230, 232, 234, 246, 252, 267, 290
Digoxin 74–5, 140, 227, 245–6, 250, 259, 261, 264–5, 274, 289
Dihydropyridine 17
Dilatation 300, 302
Dilated cardiomyopathy. *See* DCM
Dilation
  aortic root 302
  balloon 179

Diltiazem 17, 33, 64–5, 75, 204, 208–10, 245, 251, 258, 260–2, 264–5, 267, 276, 291
Dinitrate, isosorbide 232, 235
Diphtheria 241
Disability 214–5, 221–2
Disopyramide 246, 250–1, 265, 268, 290
Dissection 345
  aortic 53–4, 339, 344–5
  flow-limiting 179
  iatrogenic 344
Diuretics 204, 209–11, 229, 231, 233–4, 288
  loop 228
  potassium-sparing 228
  thiazide 204, 206–13, 228
DM 17, 25, 39–45, 48, 53, 83, 106, 122, 142–3, 154, 156, 158, 162–3, 166–7, 169–71, 173–6, 182, 189–90, 192–3, 195, 196, 200–2, 204–5, 207–10, 212–3, 214, 217, 219–21, 224, 226–7, 232, 234, 241, 247, 282, 283, 291
Dobutamine 81, 83
Docosahexaenoic acid 218
Dofetilide 249–51, 268, 290
Domperidone 290
Door-to-balloon 58, 124
Door-to-Balloon: An Alliance for Quality 90
Door-to-departure 52
Door-to-needle 50, 58
Doppler, audible venous 184
Doxazosin 210
Doxorubicin 240–1, 291
Doxycycline 328
Dronedarone 266, 269
Droperidol 290
Drug eluting stent. *See* DES
Drugs
  antiarrhythmic 229, 232, 276–7, 281, 283, 289
  anticoagulant 208–9
  antihypertensive 173, 204, 213
  antiplatelet 209
  antithrombotic 175
  beta blocker 289
  blocking 229–30
  chemotherapy 225–6
  cholesterol-lowering 194
  classes 208, 210
  illicit 225–6
  inotropic 230
  nephrotoxic 317
  nonsteroidal anti-inflammatory 229, 317
  QT-prolonging 290
  triglyceride-lowering 192
Duchenne–Becker disease 241
Duke criteria 155, 312–4
Dysbetalipoproteinemia 192
Dysfunction
  left ventricular 227, 234, 270, 278
  myocardial 129, 276
  pulmonary 143
Dyslipidemia 166, 171, 173, 202, 210, 215
  atherogenic 193
  secondary 189
Dysplasia 238
Dyspnea 157, 255, 272
Dysrhythmia 66, 178
Dystrophin 241

EBCT 336–7, 340–2
ECG 5–10, 12, 23–5, 31–3, 39, 51–4, 56, 59, 62, 66, 68–71, 81–3, 120, 154, 158, 163, 239–40, 256–9, 262, 265, 273–4, 289, 294, 336
Echocardiography 3, 6–14, 23–4, 39, 53–4, 69–71, 80–3, 137, 139, 144, 160, 162, 225, 238, 240, 252, 274, 289, 291, 294–311, 313–6, 323, 325, 340
ECMA trial 281
Edema 58, 60, 69, 70, 72–3, 202, 231
  pulmonary 160
EF 61, 73–4, 81, 87, 127, 226–7, 233–4, 271–3, 281, 297, 300–1, 305–8
Eicosapentaenoic acid 218
Ejection fraction. *See* EF
Electrical storm 287
Electrophysiological testing 275, 291
Electron beam computed tomography. *See* EBCT
Embolectomy 186
Embolism 68, 80, 83, 246, 248–9, 326, 328, 330, 344–5
  arterial 314
  pulmonary 80, 345
  recurrent 310
Embolization 302, 316, 326
Embryogenesis, normal 239
Emergency medical services systems. *See* EMS
Emerin 241
Emery Dreifuss muscular dystrophy 241
EMS 48, 50–2, 88
Enalapril 227
Encode 239–40
End-of-life 231, 233–4, 236
End-stage renal disease. *See* ESRD
End-systolic dimension. *See* SD
Endarterectomy
  carotid 138
  iliac 179–80, 183
Endocarditis 294, 308–10, 312–35
  acquisition 334
  active 314

Bartonella 318, 327–8
cause 314
culture-negative 321–2, 327, 329, 332
diagnosis 312
enterococcal 335
experimental 315, 332
infective 319–343
prophylaxis 333
prosthetic valve 293, 309, 319, 321, 325–6
enterococcal 322–5
valve
native 299 309
prosthetic 309–10
Endocrine disorders 211–2, 271, 282–3
Endocrinopathy 282
Endomyocardial fibrosis 241
Endothelin 226
Energy, estimated requirements 157
Enoxaparin 30, 32, 35–8, 42, 45, 63, 89, 127
ENRICHD Trial 221
Enterobacteriaceae 318
Enterococci 314, 316, 318, 322, 329–30
Epinephrine 75
Eplerenone 209–10, 227
Eprosartan 227
Epsilon-aminocaproic acid 141
Eptifibatide 35–7, 64, 130
Erythromycin 290
Erythropoiesis 232
Esmolol 209
Esophagogastroduodenoscopy 334
ESRD 134, 143, 219, 283, 291
Estrogens 192
Etexilate, dabigatran 254
European Atrial Fibrillation Trial 247–8
European Myocardial Infarction Amiodarone Trial 281
European Stroke Prevention Study 248
Event, thromboembolic 232
Evidence
-based grading system 332
pathological 313–4
serological 314
Exercise 6–8, 10–1, 296–7, 300–1, 303–5, 307
after cardiac rehabilitation 104
antiarrthymic effects of, after ICD 104
stress 299
testing 81, 270, 273–4, 298, 301
tolerance 305
training 98
Ezetimibe 190

Fabry disease 241
Fats, saturated 191, 218–9
Fatty acids 291
omega-3 67, 109, 217–8
polyunsaturated 189, 288
trans- 109, 189
Fenofibrate 190
Fibrate 192
Fibrillation 46, 65–6, 68, 74–5, 86
Fibrinolysis 52–3, 55–64, 68, 70, 72–3, 78–9, 82–3, 88, 124, 127
Fibroelastosis 241
First Line Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment trial 254
Fistulae 316, 325
arteriovenous 344
Flecainide 249–51, 253, 259, 261–5, 267–8
5-fluorouracil 291
Flutter, atrial 247, 252, 255, 257, 266–8, 291
Fluvastatin 190
Focal atrial tachycardias 256, 263–6
Focal junctional tachycardia 262
Folic acid 216, 220
Fondaparinux 26, 32, 35–8, 42, 45, 63, 68, 89, 127
Fosinopril 227
Framingham Heart Study 198, 205–6
Framingham Risk Score 198, 202, 205, 214–5, 338
Fugax 53
Function
impaired LV 275
renal 136
RV 274
ventricular 270, 274, 282, 289, 291
Furosemide 70, 228

Gallstones 190, 193
Gangrene 171, 182
Gaucher disease 241
Gemfibrozil 190
Genes 238–41
Genitourinary tract 332
Gentamicin 315, 317–24, 327–8
German Atrial Fibrillation Network 254
Global Registry of Acute Coronary Events 31
Glomerular filtration rate 202, 210–1
Glomerulonephritis 314
Glucocorticoid 140, 212
-remediable aldosteronism 212
Glucose 57, 64, 162, 193, 202
Glutaryl, hydroxymethyl 173
Glycohemoglobin 225
Glycoprotein 117
“golden hour” 50
Gout 190

Graft
  arterial 80
  bypass 340–1
    aortobifemoral 180, 183
    infrainguinal 169–70
  mammary artery 128
  placement 172
  sapenous vein 128–9
  synthetic 180

Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella microorganisms (HACEK) 314, 326
Halofantrine 290
Haloperidol 290
HCM 236–8, 240–2, 284
HD, structural 227, 229, 234
HDL-C 173, 188, 195, 217–9
Heart failure. *See* HF
Heart Failure ACTION Trial 103
Heart Failure Trial 273, 279, 281
Heart Outcomes Prevention Evaluation 175
Heart rate variability 279, 296
Heart Truth Campaign 222
Hematocrit 202
Hemodynamics 302
Hemorrhage 314
  intracranial 247
Heparin 26, 45, 248, 252
Hepatitis 190
Heterogeneity, genetic 238
HF 154, 158, 168, 178, 196–7, 200, 204, 206–10, 212, 238, 240–1, 245–7, 249–50, 270, 273, 278, 281, 285–6, 291–2, 294, 305, 308–10, 315–6
  congestive 60, 124, 126
  mechanical causes 71–2
  prior symptoms of 216, 229–31
  refractory
    end-stage 231–2
    symptoms 234
  symptoms 226–31, 234, 299
High density lipoprotein cholesterol. *See* HDL-C
His-Purkinje 75
History
  targeted patient 52–3
  vascular 166
HIV, parvovirus 241
Hormone
  replacement therapy. *See* HRT
  thyroid-stimulating 225
Hospice 233–4
HRT 215–6, 219, 221, 231, 291
HRV 274, 291
Hunter disease 238, 241
Hurler disease 238, 241
Hydralazine 230, 232, 233–5
Hydralazine/isosorbide dinitrate 204, 210
Hydrochlorothiazide 228
Hyper-ventilation 57
Hypercapnea 143
Hypercholesterolemia 187, 192, 219
Hypereosinophilic syndrome 241
Hyperglycemia 140, 162
Hyperhomocysteinemia 166, 171
Hyperkalemia 68, 70, 115, 211, 220, 290
Hyperlipidemia 134, 141, 192
Hyperparathyroidism 241
Hyperplasia 212
Hypertension 33–4, 42–3, 53–4, 57, 59, 64, 66–7, 126, 154, 160–1, 166–7, 169, 171, 173–4, 176, 182, 188, 196–213, 214–5, 221, 226–8, 231–2, 234, 238, 246–7, 303–4, 307–9
  defined 197, 200
  in African Americans 196
  documented 201
  episodic 201
  range 197, 199
  refractory 201, 210
  secondary 202, 345
  treatment 196, 203, 207, 210
Hyperthermia, cerebral 138
Hyperthyroidism 241
Hypertriglyceridemia 192
Hypertrophic cardiomyopathy. *See* HCM
Hypertrophy 256, 298
Hyperuricemia, hyperglycemic 190
Hypokalemia 262, 288
Hypomagnesemia 288
Hypotension 33–4, 44, 64–5, 69, 72–3, 75, 163, 211, 250
  asymptomatic 297
Hypothyroidism 189, 241
Hypovolemia 162, 164, 259
Hypoxemia 32
Hypoxia 276

IABP 70, 72–3, 78–9, 120, 139, 141
Ibuprofen 78
Ibutilide 246, 249–50, 263, 266, 269, 290
ICD 74, 78, 87, 228, 233, 235
  implantation 270–2, 275, 278–92
  selection of patients for 74
IHD 196–8, 203, 207
Illness, febrile 331–2
Imaging 25, 32–3, 39, 45, 172–3, 182, 274
  arterial 169–70
  color flow duplex 173
  computed tomography. *See* CTA

dual nuclear 340, 342
diagnostic 186
hybrid nuclear/CT 340–2
LF 274
myocardial perfusion 81, 83
noninvasive 225–6
stress, cardiac 7, 8, 11, 13
Impaired fasting glucose 106
Implantable cardioverter-defibrillator. *See* ICD
Implantation 278, 281, 286–7
Incision 334
Indapamide 228
Infants 237–9, 241
Infarct
septic pulmonary 314
size, estimating 68
Infarction 137, 139, 149, 276–7
anterior 64
bowel 141
myocardial 135–7, 139
papillary muscle 149
RV 53–4, 67, 71
Infection 169, 181–2, 185, 310, 313–4, 323, 328–31, 334–5
aortic valve 326
bloodstream 315
life-threatening 332
oral 331
prevention 335
recurrent 329, 331
reducing postoperative 140
sternal wound 140. *See also* Endocarditis
Infectious Diseases Society of America 332
Inflation, balloon 58–9, 117, 124
Inherited disorders 274
Inhibitor
angiotensin-converting enzyme 208, 212–3
cytochrome P-450 190
enzyme, converting 227–9, 234
glycoprotein IIb/IIIa 64
hydroxymethyl glutaryl-coenzyme A reductase (statins) 42
phosphodiesterase 33, 54
thrombin 254
Inotropes 231–2, 234
Instability, hemodynamic 31, 34, 40, 57–8, 61, 69, 71–2, 79, 83, 251–2
electrical 124, 126
Insufficiency
renal 123, 154, 156, 158, 163, 173, 235
valvular 313, 315
Insulin, resistance 193
Intake, sodium 226
International Society on Hypertension in Blacks 196
Intra-aortic balloon pump. *See* IABP
Intra-glomerular pressure 211
Intracranial hemorrage 56–7
Intravascular ultrasound imaging 129
Intubation, endotracheal 57
Ion, channelopathies 237, 239
Irbesartan 227
Ischemia 31–7, 39–41, 43, 61, 66–7, 72, 74–5, 78–9, 81–2, 137, 139, 144, 146–50, 160–1, 181–4, 277
acute 283
asymptomatic 120
composite endopoint 29
endpoint 30
evidence 147, 151
injury 32
limb 167–71, 179–84, 186
myocardial 61, 139, 144, 146–7, 161–3, 231, 248, 250, 262, 276–8, 291
persistent 124, 126
recurrent 26, 33–4, 37, 78, 149, 151
refractory 31
reversible 184
silent 274
symptoms 58, 171, 177–8, 185
Ischemic heart disease, *see* IHD
Isoproterenol 277, 287, 290
Isosorbide 15
Isthmus, cavotricuspid 266, 268

Jervell and Lange Nielsen syndrome 239
Junctional reciprocating tachycardia 257

KCNQ 239
Kearns-Sayre syndrome 238, 285
Korotkoff sounds 201
Kwashiorkor 241

Labetalol 227
LAD 135–6, 144, 146–9, 151
LBBB 54–5, 58–9, 61, 70–1, 274
LDL-C 108–9, 173, 187–9, 192, 217–9
Lead 240
Leaflet, bioprosthetic valve 326
Left bundle branch block. *See* LBBB
Left ventricular
noncompaction. *See* LVNC
systolic, *see* LVS
Legs and feet 166–7, 169–71, 174, 177, 180–1, 185
Lentiginosis 238, 241
Lesions 39, 40, 168, 173
Janeway's 314
pathological 314

TASC classification 186
valve 296
valvular 302, 309
Lidocaine 73, 259, 276–7
Lifestyle 203, 214–5, 219, 221
Lipid, blood 214, 288
Lipodystrophy 241
Lipoprotein 188–9, 217–8, 219
atherogenic 192
levels 188
Lisinopril 227
Liver disease 189–90
LMWH 26, 37, 45, 68, 80, 131–2, 252
Loëffler disease 241
Long QT syndrome. *See* LQTS
Losartan 227
Lovastatin 190
Low density lipoprotein cholesterol. *See* LDL-C
Low-molecular-weight heparin. *See* LMWH
Low-output syndrome 54–5, 69–72
LQTS 239, 277, 286–7, 289, 291
acquired 277
congenital 277
diagnosis 286
drug-induced 290
Lupus 241
LV 246, 274, 278, 285, 288
dilation 299–300
dysfunction 204, 208–9, 278–81, 284–6, 297, 299, 306–8
ejection fraction, *see* LVEF
pressure 299–300
size 299, 305
LVEF 17, 33–4, 40, 42–3, 61, 64, 74, 83, 137, 143, 146–7, 218, 220, 225, 227–31, 271–2, 275, 278–81, 284–6, 289, 298, 308
LVH 274
LVNC 237, 239
LVS 229, 234
LVSD 229, 234

MA 312, 330
Macroalbuminuria 210
Macrolide 190
MADIT 273, 279–80
MADIT-CRT trial 291
Magnesium 212, 225, 277, 282–3, 288, 290
salts 288
sulfate 277, 290
Magnetic resonance
angiography. *See* MRA
imaging. *See* MRI
Major ICD Secondary Prevention Trials 280
Management
BP 43, 95, 109, 112, 211
cardiac arrest 270, 275
cholesterol 187–95
dilated ascending aorta 300
DM 96, 110
HF, chronic 223, 233
hypertension 196, 203, 207, 210–2
lipid 43, 95, 109, 112–3, 187, 191, 195
patient 244–5, 255, 264–8, 270–1, 277, 285, 287, 294, 311, 339
perioperative 163–4
pharmacological 196, 249–51
physical activity 113
post-angiography 37
psychosocial 97
strategy selections 35–6
weight 25, 43–4, 94, 110, 113, 216
Markers
inflammatory 194
insulin-resistance 194
MAT 255, 257, 265
MD 271, 285, 291
MDCT 336–7, 339–44
Measurements
hemodynamic 297, 306
intracoronary physiologic 129
Mediastinitis 140, 143
Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation 254
Meningococcus 241
Mercury 240
Mesoridazine 290
Metabolic syndrome 187–8, 192–4
Methadone 290
Methylmercury 218
Metolazone 228
Metoprolol 75, 163–4, 245, 268
succinate 209, 227
tartrate 227
Mexiletine 277
MI 25, 28, 32–42, 45–90, 92, 118, 128, 137, 141, 143, 149, 154–5, 159–60, 163, 167, 173, 175, 188, 197, 200, 216, 218, 220–1, 226–9, 232, 234, 256, 258, 272–3, 278–81, 283, 292, 294
acute 137, 139, 145, 149, 280, 288
index 280
low troponin 270, 276
prevention in women 220
prior 278–81, 285–6
remote 275
Microalbuminuria 195, 202, 210

Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients 291
Mitral regurgitation. *See* MR
Mitral valve prolapse 304–5
MLP 238, 240
Moexipril 227
Monotherapy 319
Morphine 34, 54
Mortality 140–3, 146, 278, 281, 292
  arrhythmic 280
  nonarrhythmic 280
  rate, annual 11
Moxonidine 204, 210
MR 144, 281, 302–9, 311
  chronic 306
  residual 306, 308
MRA 172–3, 182–3, 336, 340, 343–6
MRI 54, 274, 299–302, 345
  cardiac 300, 302
MS 296, 302–4
Multi-detector computed tomography. *See* MDCT
Multi-Ethnic Study of Atherosclerosis 186, 342
Multicenter Automatic Defibrillator Implantation Trial. *See* MADIT
Multicenter UnSustained Tachycardia Trial. *See* MUSTT
Multifocal atrial tachycardia. *See* MAT
Murmurs 160, 294, 309
Muscle LIM protein. *See* MLP
Muscular dystrophy. *See* MD
MUSTT 273, 279–80
Mutations 238–41
  disease-causing 238
  sarcomere protein 238
MV
  apparatus and LV function 305
  gradient 304
  morphology 302
  repair 304–8
  replacement 304–6, 311
  surgery 308
MVA 303
Mycotic aneurysm. *See* MA
Myocardial infarction. *See* MI
Myocarditis 237–8, 241–2, 282
Myocardium 60–1, 72, 78–9, 81, 137, 145, 147, 149–51, 236–7, 239, 241–2
Myocytes 238, 241
Myotonic disease 241

N-acetylcysteine 173
Nadolol 227
Nafcillin 320–1
  oxacillin-susceptible 320–1
Naproxen 85
National Cholesterol Education Program. *See* NCEP
National Cognitive and Skills examination 104–5 104
National Heart Lung and Blood Institute 222
National Heart, Lung, and Blood Institute. *See* NHLBI
Naxos disease 239
NCEP 48, 174, 176, 182, 187, 338
NCEP-ATP3 103
Necrosis, myocyte 242, 276
Nephropathy, overt diabetic 210
Nephrotic syndrome 192
Neurofibromatosis 238, 241
Neurohormones 226
Neuromuscular disease 240, 284
Neuropathy 174
NHANES III 199, 200
NHLBI 166
  Obesity Education Initiative 191
Niacin 219
NICM 272, 279
Nicotinic acid 190, 192–3
Nieman–Pick disease 241
Nifedipine 65
Nitrates 17–8, 34, 54, 67, 70, 78–9, 208–9, 230, 232
Nitrogen, blood urea 225
Nitroglycerin. *See* NTG
Nodosa, polyarteritis 344
Nondihydropyridine 212
Nonparoxysmal junction tachycardia 262–3
Nonsteroidal anti-inflammatory drugs. *See* NSAIDs
Noonan syndrome 238, 241
Norepinephrine 226
NSAIDs 26, 33, 54, 78, 85
NSTEMI 118, 145, 147–9
NTG 28, 31, 33–4, 41, 48, 54, 66–7, 162
  intraoperative 162
  intravenous 54
  sublingual 48, 84
Nutritional counseling 94

Obesity 188–9, 191–3, 214, 221, 234, 270, 283
Occlusion, arterial 168–9, 179–80, 182–3, 185–6
Off-pump CABG. *See* OPCAB
Olmesartan 227
OPCAB 137–8, 142, 145
Osler's nodes 314
Outpatient parenteral antibiotic therapy 331
Oxacillin 320–1
Oximetry, pulse 33, 66
Oxygen, supplemental 33, 54, 66, 68, 70
Oxygenation 290
Oxygenator, membrane versus bubble 138

Pacemaker 282–3, 285, 291
Pacing 277, 290
  biventricular 274, 286
  long-term 277
  requirement 291
  ventricular 290
PAD 92, 165–79, 182–6, 204–5, 215–20
  asymptomatic 165, 167, 171, 175
  diagnosis 170, 174, 176
  stenosis 172
  symptomatic 175
Pain
  chest 46, 48, 50–1, 53–4, 71–2, 75, 78
  postprandial abdominal 166
Palpitations 272, 275, 284, 288
Parathyroid disease 202
Paroxysmal supraventricular tachycardia 256
Pathway, accessory 256, 258, 263, 275
Patients
  African-American 203–4, 210–3
  asymptomatic 229, 235, 282, 293, 294, 296–300, 302–8, 311, 339, 342
  asymptomatic post-MI 206
  burn 329
  dialysis 143
  elderly 142, 232, 270, 289
  hemodialysis 344
  overweight 212
  pediatric 275, 289
  post-CABG 141
  post-infarction 271–2
  post-MI 271, 281, 291
  stratified 313
  transplant 145
  women. *See* Women
  young 289
PCI 52, 57, 61, 70, 73, 78, 92, 104, 117–33, 137, 144–6, 149, 158–60,
    after fibrinolysis 127
    vs. CABG 347–51
  cardiogenic shock 127–8
  and exercise in symptomatic CAD 104
  primary 57–9
    as an alternate to thrombolysis 128
    for STEMI 120
  recommendations 112–5
  rescue 60, 126–7
Pellagra 241
Penbutolol 227
Penicillin 315, 317–25, 327, 333, 335
Penindopril 227
Pentamidine 290
Pentoxifylline 177–8, 181
Peptic ulcer disease 190
Peptides, B-type natriuretic 25
Percutaneous
  coronary intervention. *See* PCI
  mitral balloon valvotomy. *See* PMBV
  transluminal coronary angioplasty. *See* PTCA
Perforation 294, 309, 325–6, 333
Pericarditis 78
Peripheral arterial disease, thromboembolic. *See* PAD
PET-CT 340
Pharmaco-H1 279
Pharmacokinetics, altered 289
Pharmacotherapy 43–4, 218–9
Pheochromocytoma 212, 238, 240
Phlegmasia cerulea dolens 182–4
Pimozide 290
Pindolol 227
Placebo 247–8, 281
Plakoglobin 239
Plakophillin-2 239
Pneumonia 143, 329–30
POISE group 163
Polycystic ovarian syndrome 193
Pompe disease 238, 241
Potassium 282–3, 288
  repletion 277, 290
  serum 202, 207, 209–10, 288, 290
Prasugrel 45
Pravastatin 190
Preeclampsia 212
Preexcitation syndrome 246–7
Pregnancy 211–2, 268–9, 289
Prehypertension 197–200
Pressure
  intracranial 57
  pulmonary artery 295, 302–8
Presyncope 255, 272, 275
Prevention of Arterial Thromboembolism in Atrial Fibrillation 248
Proarrhythmia 253, 256
Procainamide 72–3, 246, 250–1, 259, 263, 265, 267–8, 276–7, 290
Profile
  genetic 239
  lipid 202
Progestins 189
Propafenone 249–51, 253, 261–5, 267–8
Prophylaxis 287, 332–5
  antibiotic 331–4
  primary 284
  rheumatic fever 296
Propranolol 227, 245, 262, 268
Prosthesis, mechanical 310–1

Protamine 57
Protection
  devices, distal embolic 128–9
  myocardial 138–9
Protein, myosin binding 238, 240
Proteinuria 211–2
Pseudomonas 318, 323, 329
Pseudoaneurysms 316
PTCA 135–6, 143, 150
Pulmonary arterial hypertension 282
Pulse volume recording 182–3
PURSUIT 32
PVCs 274–5, 282, 289
Pyrexia 259

Questionnaire, Rose 171
Quinapril 227
Quinidine 250, 268, 287, 290

Radiation 340, 342
Radiculopathy 174
Radiofrequency Ablation in Paroxysmal Atrial Fibrillation 254
Radionuclide ventriculography 301
Ramipril 227
Randomized Evaluation of Long Term Anticoagulant Therapy trial 254
Receptor, angiotensin 291
Recommendations for Blood Pressure Measurement in Humans and Experimental Animals 196, 200
Regurgitation 294, 299–300, 309–10, 326
  aortic 282, 294–6, 299, 301
  mitral 281, 302–9, 311
  valvular 296, 313–4
Rehabilitation, cardiac 44, 87
RELY trial 254
Renal failure, chronic 169, 182, 189, 192
Renin-angiotensin-aldosterone system 42, 64, 68, 114–5
Renovascular disease 202
Reoperation 139, 142, 144, 151
Reserve, vasodilatory 129
Respiratory gas exchange, measuring 225
Response
  hemodynamic 300–3
  ventricular 245–6, 250
Restenosis 129, 132
Resuscitation 291
Resuvastatin 190
Resynchronization, cardiac 233
Reteplase 57
Retinoids 192
Retinopathy 202
Revascularization 11, 21–3, 25–6, 37, 39–40, 57, 72, 78, 122, 124, 128, 136–7, 139, 143, 145, 149–51, 153, 158, 160, 167–9, 172, 177, 179–82, 184–6, 225, 231–2, 248, 277–8, 283, 338
  percutaneous 24
Rheumatic disease 282
Rhythm, idioventricular 73
Rickettsia 241
Rifampin 321, 327–8
Right ventricular infarction. *See* Infarction, RV
Risk
  absolute 219, 221, 246
  assessment 187–9, 194–5, 284–5, 337
    Framingham 198, 202, 205, 214–5, 338
    Reynolds 214
  atherosclerotic 187
  CAD 338–9, 343
  cardiac 153–7, 160–1
  cardiovascular 165–6, 168–9, 173, 180, 186, 197–202, 206, 210, 340, 343
  categories 188–9
  clinical 153–6, 158, 161
  CV 227
  CVD "lifetime" 214, 221
  embolization 326
  factors 140, 142–3, 247, 249, 253, 273, 284–5, 291
  high 339
  ischemic 154–5
  management 188, 194
  neurologic 138
  noncardiac 158
  operative 141, 144
  perioperative 153–4
  prediction 338
  predictors 291
  procedural 142
  profile 187
  ratio 337
  reduction 191
  relative, early invasive vs. conservative therapies 38
  stratification 11, 13, 31, 38–39, 81, 136, 275, 287, 342
    cardiac 157
    post MI 291
  stroke 134, 138, 144
Rivaroxaban 254
Rocky Mountain spotted fever 241
Romano–Ward syndrome 239
Root, aortic 300–2
Roth's spots 314
Rupture
  free wall 69, 71, 149
  papillary muscle 69, 71
  postinfarction ventricular septal 149

RV 134, 139
RyR2 (cardiac ryanodine receptor) 239–40

S. agalactiae 329
SAI-P 336
Salbutamol 259
Salicylates 85
Salmonella 318
Sarcoglycan 241
Sarcomere 238
Saturation, arterial oxygen 66
SBP 197–200
  lowering 205
SCAI 117, 165
SCD 271, 273–5, 278, 283–9
SCD-HeFT 273, 279, 281
Sciatica 174
Scintigraphy, adenosine stress perfusion nuclear 83
Sclerosis 238, 241
  glomerular 211
SCN5A 239–40
SCORE 195, 221
Scurvy 241
SD 300–1, 305–8
Selective estrogen-receptor modulators 220
Selenium 240–1
Severity
  hemodynamic 296, 302, 304, 309
  regurgitative 300
  valve disease 294–5
Shock 26, 33–4, 61, 149, 275
  cardiogenic 57, 59, 69–71, 149
Short QT syndrome 239–40
Shunts 294, 309
Signal-averaged ECG 279
Sildenafil 33
Simvastatin 190
Single-photon emission computed tomography 54, 279, 348
Sinus 17, 75, 78, 250–4, 255–60, 264, 266, 272, 277, 286
Sinusoids 239
Skin, infected 334–5
Sleep disorders 85, 87. *See also* Apnea, sleep
Sodium 317–9, 322–3
  channel blocker 291
  dietary 203, 211
Sotalol 140, 250–1, 253, 259, 261–2, 264–5, 267–8, 276, 279–80, 285–6, 290
Sparfloxacin 290
Sphygmomanometer 201
SPINAF 247–8
Spironolactone 210, 227–8, 235
SR 256, 258, 260, 266
Staphylococci 314, 316, 318, 320–1, 329, 334–5
Statins 139, 190, 195, 291
STEMI 46–9, 50–9, 61, 63–90, 118, 120, 124–8, 134, 145, 149, 209, 242
  arrhythmias after 72
  catheterization and revascularization following 82
  and the CCU 66
  convalescence, discharge, and post-MI care 81, 83–4
  initial evaluation 52
  interventions 60
  ischemia/infarction management after 79
  onset 50
  psychosocial impact 85
  reperfusion 51, 56
  risk factors 47–8
  symptoms 48, 50–3, 55–6, 58, 60–2, 66, 74, 82, 84–5, 87–8, 90
Stenosis 17, 37, 39, 40–1, 45, 61, 80–1, 123, 127, 137–8, 146–9, 151, 172, 179, 185, 238, 246, 341, 343, 345
  aortic 144
  carotid 138
  coronary 147, 341, 343
  mitral 295, 302–3
  renal artery 345
  rheumatic mitral 246
  valvular 228
  vein graft 144
Stent 26, 28, 41–2, 45, 64, 68, 86, 159–60, 179, 249
  bare-metal 132
  paclitaxel-eluting 249
  restenosis 129
  sirolimus-eluting 249
Sternotomy 150
Steroids, anabolic 189
Strains 318, 320–2, 324–5, 329, 335
Strategy
  ACC/AHA initial invasive 41
  invasive 35–7, 56, 59
    vs. conservative 37–9, 123
Streptococci 318, 329, 334
  B-Hemolytic 329, 334–5
  bovis 314, 316–9
  nutritionally variant 329
  viridans 314–9, 325, 335
Streptokinase 79
Streptomycin 323
Stress 32, 33, 39
  echocardiographic 340
  pharmacological 39, 274
Stroke 53, 60, 137–8, 140–1, 143–5, 163, 188, 197–8, 202, 212, 214, 216, 218, 220–1, 246–9, 254, 305, 344–5
  hemorrhagic 208, 216
  incidence 200

ischemic 57, 79, 80, 216, 247–9
mortality rate 198
prevention 247–8, 254
Stroke Prevention with the Oral Direct Thrombin Inhibitor Ximelagatran 254
"Subclavian steal syndrome" 345
Suction, cardiotomy 138
Sudden cardiac death 270–92
Sudden Cardiac Death in Heart Failure Trial. *See* SCD-HeFT
Sudden unexplained nocturnal death syndrome. *See* SUNDS
Sulfonamides 241
SUNDS 237, 239–40
Supplements, antioxidant vitamin 216, 220
Support
inotropic 69, 71
vasopressor 69, 70
Supraventricular arrhythmias 255–69
Supraventricular tachycardia. *See* SVT
Surgery
bypass 144
coronary 146
mitral valve prolapse 293
noncardiac 154–5, 163
nonvascular 155
urgent/emergent 163
valve 142, 144
vascular 152, 155, 158, 160–1, 163
Survival 135–6, 139, 142–3, 145–8, 278, 281–9
SVT 256, 258–9, 268–9
Syncope 239–40, 255, 270, 272, 274–5, 278, 282, 284–8, 294
SYNERGY 29
Systematic Coronary Risk Evaluation 195, 221
Systolic blood pressure. *See* SBP

T-wave alternans. *See* TWA
Tachyarrhythmia 275, 287
supraventricular 286
ventricular 71
Tachycardia 17, 34, 54, 64–5, 67, 75, 160, 164, 240, 255–7, 259–64, 268–9, 273, 284, 289, 291
atrial flutter 266
atrioventricular reciprocating 256–8, 260–2, 264
focal atrial 256, 263–6
focal junctional 262
mechanism 266
nonparoxysmal junction 262
pathway-mediated 255
QRS 256–61, 275–6, 284, 286
sinus 55, 259–60
ventricular 150, 271–2, 276, 285
recurrent 281
Tadalafil 33
Tafazzin 241
Tako-tsubo 236–7, 242
Tamponade, pericardial 69
TASC 166, 185
TBI 165, 168, 170, 176, 182–3
TEE 182–3, 252, 267, 313–4, 316
Telmisartan 227
Tenecteplase 57
Testing
Allen's 167
liver function 225
noninvasive stress 38
pharmacological stress 39. *See also* Exercise
Therapy 226, 230, 232–5
5-fluorouracil 291
ablative 266
adjunctive 181, 275, 285
antiplatelet and antithrombotic 117, 130–2
aldosterone blocking 109
alternative 225–6
amiodarone 284
analgesic 32
ancillary 62, 127
anti-anginal 23
antiarrhythmic 72–3, 250–4, 286–8
antibiotic 309–10, 313–5, 318, 321–3, 331–2
anticoagulation 34, 37–8, 45, 57, 62–3, 68, 127, 175, 246–8, 252
antihypertensive 173, 196–7, 200–1, 206–8
anti-ischemic 32
antiplatelet 28, 34–7, 41, 45, 57, 84, 141, 167–8, 174–6, 185–6, 335
antithrombotic 28, 35–7, 86, 246–8
arrhythmic 271. *See also* Arrhythmia
behavior modification 175
beta-blocker 17, 25–6, 33–4, 42–3, 46, 55, 64, 66–7, 70, 78, 87, 114, 116, 139–40, 152, 155–6, 160–1, 163–4, 206–10, 213, 217, 220, 227, 229–30, 232–5, 245–6, 251, 259, 261–5, 267, 276–8, 281, 286–8, 291
cardiac resynchronization 230, 292
ceftriaxone 318
cholesterol-lowering 187–91
clopidogrel. *See* Clopidogrel
conservative 38
"destination" 231
diabetic 175
dietary 191. *See also* Diet
digoxin 268
double beta-lactam 335
drug 190–2, 194, 258, 260, 262, 266–8, 275, 285, 288
endovascular 177
evidence-based 232
fibrate 219

fibrinolytic 52, 55–60, 63, 68, 70, 78–9, 82–3, 88, 126, 140
fluoroquinolone 326
gentamicin 317, 319
glucose control 175
ICD 230–1, 233–4, 272, 278, 281, 284–6, 289–91
invasive 38, 122, 168
LDL-lowering 187, 189, 191–2
lifestyle 190, 194, 219
lipid-lowering 189, 338–9
nicotine replacement 175
nitrate 162
noninvasive 147
nutritional 191
parenteral 331
pharmacological 19, 87, 141, 245–6, 252–4, 289
prophylactic 179
reperfusion 47–8, 53–7, 59, 61–4, 68–9, 71, 78, 81–3, 88, 90
risk-reduction 189
salvage 179
shock 276
statin 161, 164, 288
stem cell 292
steroid 202
surgical 168, 182, 186, 322
thienopyridine 160
vancomycin 317–9, 322–4, 327
vasodilator 299
Thiazide 109, 204
Thickness, carotid intimamedia 342
Thienopyridine 26, 63, 68, 117
Thioridazine 290
Thrombin 254
Thrombocytopenia 62–3
Thromboembolism 182–3, 246–9, 252, 254, 294
arterial 248
preventing 244, 246, 248, 254
Thrombosis 45, 181, 184, 344
catheter 63, 127, 181
leg bypass graft 184
mesenteric vein 345
in myocardial infarction 26, 31
venous 345
Thrombus 81, 86, 252
atrial 302–5
Thyroid disease 202
TIA 138, 188, 202, 246
Ticlopidine 84, 141
Timolol 227
Timothy syndrome 239
Tirofiban 35–7, 64
Tirofibran 130
Titin 240
Tobacco 44, 97, 109, 112, 141–2, 166–7, 170–1, 173, 175, 188, 192–3, 202, 214–5, 218, 229
Toe-brachial index. *See* TBI
Torsades de pointes 277, 287, 290–1
Torsemide 70, 228
Total cardiac mortality 286
Toxicity 290
blocker-related 291
cardiac 290
digoxin 288
drug-induced 291
TR 308
Trandolapril 227
Tranexamic acid 141
Transaminase, liver 254
TransAtlantic Inter-Society Consensus. *See* TASC
Transesophageal echocardiography. *See* TEE
Transfusion 140–1
Transient ischemic attack. *See* TIA
Transmyocardial surgical laser revascularization 145–6
Transplantation, renal 283
Transthoracic echocardiography. *See* TTE
Treadmill 23, 178
Triage, strategies for ER 52
Trial of Preventing Hypertension 200
Triamterene 228
Triglycerides 173, 187–9, 192–3, 195, 218
Troponins 25, 31–2, 37, 45, 53, 118, 123, 139, 160, 163, 238, 240–1
Trypanosome cruzi 240
TTE 313–4, 316, 331
Turbulence 274, 291
TWA 272, 274, 291
Typhus 241

UA 33–45, 209
UA/NSTEMI 25–45, 90, 122–24, 147–8, 158
causes 122
diagnosis 35–6
early invasive versus conservative therapy 125
medications 25, 33–4, 41–2, 131
recommendations 25–30
revascularization with PCI and CABG 39–41
UFH 62, 80, 127, 131–2
UK-TIA 248
Ultrasonography 129, 137, 165, 169, 172, 174
Unfractionated heparin. *See* UFH
Urinalysis 202, 225
US Renal Data System 211

VA 60–1, 72–4, 270–92
Vaccine 335
influenza 109, 114–6

Valsartan 64, 68, 209, 227
Valve 296, 308, 310–1
  aortic 297–8, 300–1, 310–1
  bicuspid 302
  calcification 297–9
  cardiac, repair 294
  disease 294–5
  gradients 296
  mechanical heart 246–7
  mitral 281, 304, 306–8, 311
  morphology 299, 302–4
  native 309–10, 315, 317–8, 328
    332 334 322–23, 326, 330
  nonpliable calcified 304
  prosthetic 309–10, 315, 329, 313–4, 319, 322–8, 330
  repair 304
    replacement 92, 293, 297–8, 300–1
  resection 315
  surgery 306, 308–9, 322
  tricuspid 308
Valvotomy
  aortic balloon 298
  percutaneous mitral balloon 302–4
Valvular heart disease 293–311
Valvulopathy 294
Vancomycin 317–9, 318–25, 327–8, 335
Varapamil 204
Vardenafil 33
Vasculitis 344–5
Vasculopathy, allograft 145
Vasodilation 162
Vasopressin 69, 75
Vegetation 313–4, 316, 326, 330
Vein
  autogenous 180–1, 185
  iliac 345
  pulmonary 253–4
Venography 345
Ventricular
  arrhythmia. *See* VA
  fibrillation. *See* VF
  septal rupture. *See* VSR
  tachyarrhythmia. *See* VT
Ventriculography 39
  contract 83
  left 13
  radionuclide 225
Verapamil 17, 33, 64–5, 75, 204, 208–10, 245, 251, 258–61, 264–5, 267–8, 276, 289, 291
Verapamil/diltiazem 259
Very low density lipoprotein 187
VF 72, 74, 275, 278, 280, 283–5, 289
Vitamin 216, 220, 246–7, 249, 252
VSR 46, 53, 55, 57, 60–1, 64, 66, 69, 71–3, 75, 78, 81, 83
VT 256–9, 261, 268, 275–9, 282–3, 285–6, 288–9
  ablation 275, 277
  catecholaminergic 273
  idiopathic 277, 287
  monomorphic 275, 280–2, 288
  non-sustained spontaneous 285
  polymorphic 277, 283
  recurrent 276, 281, 290
  refractory 288
    polymorphic 73
  septal 289
  stable 280–1, 286
  storm 277
  sustained 292–5 275–6, 280, 282, 284–5, 288–9
  symptomatic 288
  unresponsive 279
  unstable 285, 289

Warfarin 80, 84, 86, 110, 114, 137, 140, 175, 186, 234, 248–9, 254, 305, 310–1
WAVE trial 186
Weight 202–4, 212
  management 25, 43–4, 94, 110, 113, 216
Whipple disease 241
WISE Study 221
Wolff–Parkinson–White syndrome 263, 274–5
Women 13, 24, 26, 37, 44–5, 141–2, 144, 188, 192–4, 199, 203, 205–6, 209–10, 214–22, 247, 337–9, 342
  CVD prevention 215–21
  pregnancy 211–2, 268–9, 289
WomenHeart 222
Working Group on Myocardial and Pericardial Diseases 242

X-linked DCM 241
Ximelagatran 253–4

Z-disc protein-encoding genes 240
ZASP 240

Author Disclosure Table

Working group member	Employment	Research grant	Other research support	Speakers bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Antman	Harvard Medical School	Merck & Co, Inc*, Bristol-Myers Squibb Pharmaceutical Research Institute*, Millenium Pharmaceuticals*, Nuvelo, Inc*, AstraZeneca Pharmaceuticals LP*, CV Therapeutics*, Inotek Pharmaceuticals Corporation*, Schering-Plough Research Institute*, Integrated Therapeutics Corporation*, Bayer Healthcare LLC* Ortho-Clinical Diagnostics, Inc*, Sanofi-Synthelabo Recherche*, GlaxoSmithKline*, Amgen, Inc*, Beckman Coulter, Inc*, Biosite Incorporated*, Roche Diagnostics Corporation*, Roche Diagnostics GmbH*, Pfizer, Inc*, Accumetrics, Inc*, The National Institutes of Health*, Novartis Pharmaceuticals*, Sanofi-Aventis+, Eli Lilly and Company+, Daiichi Sankyo+	None	Sanofi-Aventis*, Eli Lilly and Company*,	None	None	Sanofi-Aventis*, Momenta Pharmaceuticals, Inc*	None
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Wilson	Mayo Clinic	None	None	None	None	None	None	None
Zipes	Indiana University School of Medicine	Medtronic+	None	None	None	Physical Logic*	Medtronic+, Physical Logic*	None

*Modest.
+Significant.
This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire which all writing group members are required to complete and submit. A relationship is considered to be "Significant" if (a) the person receives $10,000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.