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ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)

Developed in Collaboration With the Canadian Cardiovascular Society

WRITING COMMITTEE MEMBERS

Elliott M. Antman, MD, FACC, FAHA, *Chair*

Daniel T. Anbe, MD, FACC, FAHA
Paul Wayne Armstrong, MD, FACC, FAHA
Eric R. Bates, MD, FACC, FAHA
Lee A. Green, MD, MPH
Mary Hand, MSPH, RN, FAHA
Judith S. Hochman, MD, FACC, FAHA
Harlan M. Krumholz, MD, FACC, FAHA
Frederick G. Kushner, MD, FACC, FAHA
Gervasio A. Lamas, MD, FACC
Charles J. Mullany, MB, MS, FACC
Joseph P. Ornato, MD, FACC, FAHA
David L. Pearle, MD, FACC, FAHA
Michael A. Sloan, MD, FACC
Sidney C. Smith, Jr., MD, FACC, FAHA

TASK FORCE MEMBERS

Elliott M. Antman, MD, FACC, FAHA, *Chair*
Sidney C. Smith, Jr., MD, FACC, FAHA, *Vice Chair*

Joseph S. Alpert, MD, FACC, FAHA*
Jeffrey L. Anderson, MD, FACC, FAHA
David P. Faxon, MD, FACC, FAHA
Valentin Fuster, MD, PhD, FACC, FAHA
Raymond J. Gibbons, MD, FACC, FAHA*†
Gabriel Gregoratos, MD, FACC, FAHA*
Jonathan L. Halperin, MD, FACC, FAHA
Loren F. Hiratzka, MD, FACC, FAHA
Sharon Ann Hunt, MD, FACC, FAHA
Alice K. Jacobs, MD, FACC, FAHA
Joseph P. Ornato, MD, FACC, FAHA

*Former Task Force Member
†Immediate Past Chair

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The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated and reviewed by the writing committee as changes occur. See Appendix 1 for relationship with industry information for writing committee members; see Appendix 2 for peer reviewer names and relationships with industry for this document.

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TABLE OF CONTENTS

1. Preamble 3
1.1. Introduction..... 4

2. Pathology..... 8
2.1. Role of Acute Plaque Change..... 8
2.2. Acute Coronary Syndromes..... 8
2.3. Pathophysiology..... 8
2.4. Epidemiology..... 9

3. Management Before STEMI..... 10
3.1. Identification of Patients at Risk of STEMI..... 10
3.2. Interventions to Reduce Risk of STEMI..... 10
3.3. Patient Education for Early Recognition and Response to STEMI..... 11

4. Onset of STEMI..... 12
4.1. Recognition of Symptoms by Patient..... 12
4.1.1. Silent and Unrecognized Events..... 15
4.2. Out-of-Hospital Cardiac Arrest..... 15

5. Prehospital Issues..... 16
5.1. Emergency Medical Services Systems..... 16
5.2. Prehospital Chest Pain Evaluation and Treatment..... 17
5.3. Prehospital Fibrinolysis..... 18
5.4. Prehospital Destination Protocols..... 24

6. Initial Recognition and Management in the Emergency Department..... 25
6.1. Optimal Strategies for Emergency Department Triage 25
6.2. Initial Patient Evaluation..... 25
6.2.1. History..... 26
6.2.2. Physical Examination..... 27
6.2.2.1. Differential Diagnosis..... 28
6.2.3. Electrocardiogram..... 28
6.2.4. Laboratory Examinations..... 30
6.2.5. Biomarkers of Cardiac Damage..... 30
6.2.5.1. Bedside Testing for Serum Cardiac Biomarkers..... 32
6.2.6. Imaging..... 34
6.2.7. Global Risk Assessment Tools..... 34
6.3. Management..... 35
6.3.1. Routine Measures..... 35
6.3.1.1. Oxygen..... 35
6.3.1.2. Nitroglycerin..... 35
6.3.1.3. Analgesia..... 36
6.3.1.4. Aspirin..... 36
6.3.1.5. Beta-Blockers..... 37
6.3.1.6. Reperfusion..... 38
6.3.1.6.1. General Concepts..... 38
6.3.1.6.2. Selection of Reperfusion Strategy..... 41
6.3.1.6.3. Pharmacological Reperfusion 44
6.3.1.6.4. Percutaneous Coronary Intervention..... 55
6.3.1.6.5. Acute Surgical Reperfusion... 66
6.3.1.6.6. Patients With STEMI Not Receiving Reperfusion..... 67
6.3.1.6.7. Assessment of Reperfusion.... 67
6.3.1.6.8. Ancillary Therapy..... 67
6.3.1.6.9. Other Pharmacological Measures..... 76

7. Hospital Management..... 82
7.1. Location..... 82
7.1.1. Coronary Care Unit..... 82
7.1.1.1. Monitoring and Treatment for Adverse Events..... 83
7.1.2. Stepdown Unit..... 83
7.2. Early, General Measures..... 84
7.2.1. Level of Activity..... 84
7.2.2. Diet..... 84
7.2.3. Patient Education in the Hospital Setting..... 85
7.2.4. Analgesia/Anxiolytics..... 86
7.3. Risk Stratification During Early Hospital Course..... 87
7.4. Medication Assessment..... 88
7.4.1. Beta-Blockers..... 88
7.4.2. Nitroglycerin..... 89
7.4.3. Inhibition of the Renin-Angiotensin-Aldosterone System..... 89
7.4.4. Antiplatelets..... 90
7.4.5. Antithrombotics..... 91
7.4.6. Oxygen..... 92
7.5. Estimation of Infarct Size..... 92
7.5.1. Electrocardiogram Techniques..... 92
7.5.2. Cardiac Biomarker Methods..... 92
7.5.3. Radionuclide Imaging..... 93
7.5.4. Echocardiography..... 93
7.5.5. Magnetic Resonance Imaging..... 93
7.6. Hemodynamic Disturbances..... 93
7.6.1. Hemodynamic Assessment..... 93
7.6.2. Hypotension..... 94
7.6.3. Low-Output State..... 95
7.6.4. Pulmonary Congestion..... 95
7.6.5. Cardiogenic Shock..... 98
7.6.6. Right Ventricular Infarction..... 100
7.6.7. Mechanical Causes of Heart Failure/Low-Output Syndrome..... 102
7.6.7.1. Diagnosis..... 102
7.6.7.2. Mitral Valve Regurgitation..... 104
7.6.7.3. Ventricular Septal Rupture After STEMI..... 104
7.6.7.4. Left Ventricular Free-Wall Rupture.... 105
7.6.7.5. Left Ventricular Aneurysm..... 105
7.6.7.6. Mechanical Support of the Failing Heart..... 106
7.6.7.6.1. Intra-Aortic Balloon Counter-pulsation..... 106
7.6.7.7. Cardiac Transplantation After STEMI 106
7.7. Arrhythmias After STEMI..... 107
7.7.1. Ventricular Arrhythmias..... 107
7.7.1.1. Ventricular Fibrillation..... 107
7.7.1.2. Ventricular Tachycardia..... 108
7.7.1.3. Ventricular Premature Beats..... 110
7.7.1.4. Accelerated Idioventricular Rhythms and Accelerated Junctional Rhythms..... 110
7.7.1.5. Implantable Cardioverter Defibrillator Implantation in Patients After STEMI. 110
7.7.2. Supraventricular Arrhythmia/AF..... 112
7.7.3. Bradyarrhythmias..... 116
7.7.3.1. Acute Treatment of Conduction Disturbances and Bradyarrhythmias... 116
7.7.3.1.1. Ventricular Asystole..... 118
7.7.3.2. Use of Permanent Pacemakers..... 120
7.7.3.2.1. Permanent Pacing for Brady-cardia or Conduction Blocks Associated With STEMI..... 120
7.7.3.2.2. Sinus Node Dysfunction After STEMI..... 121

7.7.3.2.3. Pacing Mode Selection in Patients With STEMI 121
7.8. Recurrent Chest Pain After STEMI..... 122
7.8.1. Pericarditis.....122
7.8.2. Recurrent Ischemia/Infarction.....123
7.9. Other Complications..... 124
7.9.1. Ischemic Stroke.....124
7.9.2. Deep Venous Thrombosis and Pulmonary Embolism.....127
7.10. Coronary Artery Bypass Graft Surgery After STEMI127
7.10.1. Timing of Surgery..... 127
7.10.2. Arterial Grafting.....128
7.10.3. Coronary Artery Bypass Graft Surgery After Fibrinolytic Therapy..... 128
7.10.4. Coronary Artery Bypass Graft Surgery for Recurrent Ischemia After STEMI.....129
7.10.5. Case Selection Concerns in CABG After STEMI..... 129
7.10.6. Elective CABG After STEMI in Patients With Angina.....129
7.10.7. Coronary Artery Bypass Surgery After STEMI and Antiplatelet Agents.....129
7.11. Convalescence, Discharge, and Post-MI Care.....130
7.11.1. Risk Stratification at Hospital Discharge.....131
7.11.1.1. Role of Exercise Testing.....131
7.11.1.2. Role of Echocardiography..... 134
7.11.1.3. Exercise Myocardial Perfusion Imaging..... 135
7.11.1.4. Left Ventricular Function.....136
7.11.1.5. Myocardial Viability..... 136
7.11.1.6. Invasive Evaluation.....137
7.11.1.7. Ambulatory ECG Monitoring for Ischemia..... 137
7.11.1.8. Assessment of Ventricular Arrhythmias.....138
7.12. Secondary Prevention.....139
7.12.1. Patient Education Before Discharge.....139
7.12.2. Lipid Management.....141
7.12.3. Weight Management.....143
7.12.4. Smoking Cessation.....144
7.12.5. Antiplatelet Therapy.....145
7.12.6. Inhibition of the Renin-Angiotensin-Aldosterone System.....145
7.12.7. Beta-Blockers.....147
7.12.8. Blood Pressure Control.....148
7.12.9. Diabetes Management.....148
7.12.10. Hormone Therapy.....149
7.12.11. Warfarin Therapy.....150
7.12.12. Physical Activity.....151
7.12.13. Antioxidants.....153

8. Long-Term Management.....153
8.1. Psychosocial Impact of STEMI.....153
8.2. Cardiac Rehabilitation.....155
8.3. Follow-Up Visit With Medical Provider.....155
8.4. Return to Work and Disability.....156
8.5. Other Activities.....158

Appendix 1: Writing Committee Relationship Disclosures..159

Appendix 2: Peer Reviewer Relationship Disclosures.....161

Appendix 3: Abbreviations.....167

References.....169

1. PREAMBLE

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and generally have a favorable impact on the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up. When available, information from studies on cost will be considered, however review of data on efficacy and clinical outcomes will be the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated and reviewed by the writing committee as changes occur.

These practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all of the circumstances pre-

sented by that patient. There are circumstances where deviations from these guidelines are appropriate.

The executive summary and recommendations are published in the August 4, 2004, issue of the Journal of the American College of Cardiology and August 3, 2004, issue of Circulation. The full text is published on the ACC and AHA World Wide Web sites. Copies of the full text and the executive summary are available from both organizations.

Elliott M. Antman, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

1.1. Introduction

The process of guideline development for management of patients with acute myocardial infarction (AMI) has undergone substantial evolution since the inaugural publication entitled "Guidelines for the Early Management of Patients with Acute Myocardial Infarction" in 1990 under the auspices of the ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Chairman, Dr. Rolf Gunnar; Figure 1) (1). Subsequently, the ACC/AHA Task Force on Practice Guidelines convened a committee (Chairman, Dr. Thomas J. Ryan) in 1994 to revise the 1990 guidelines. In the 1996 guideline publication, "ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction," the term acute coronary syndrome was used, reflecting the emerging overarching concept that disruption of a vulnerable or high-risk plaque causes an episode of ischemic discomfort (2). Emphasis was placed on the 12-lead electrocardiogram (ECG) that was used to categorize patients into 2 broad cohorts: those presenting with ST elevation and those presenting without ST elevation (ultimately diagnosed as unstable angina or non–Q-wave myocardial infarction (MI) depending on whether a biomarker of necrosis was detected in the patient's blood). The 1996 guidelines discussed the management of both the ST-elevation and non–ST-elevation presentations of the acute coronary syndromes. The same approach was taken in the 1999 update of the guideline (also chaired by Dr. Ryan) that was posted as an electronic update on the ACC and AHA World Wide Web sites (3).

In parallel to the above efforts, in 1994, the Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute jointly published guidelines for the diagnosis and management of patients with unstable angina (Chairman, Dr. Eugene Braunwald). In recognition of rapid advances in the understanding and management of patients

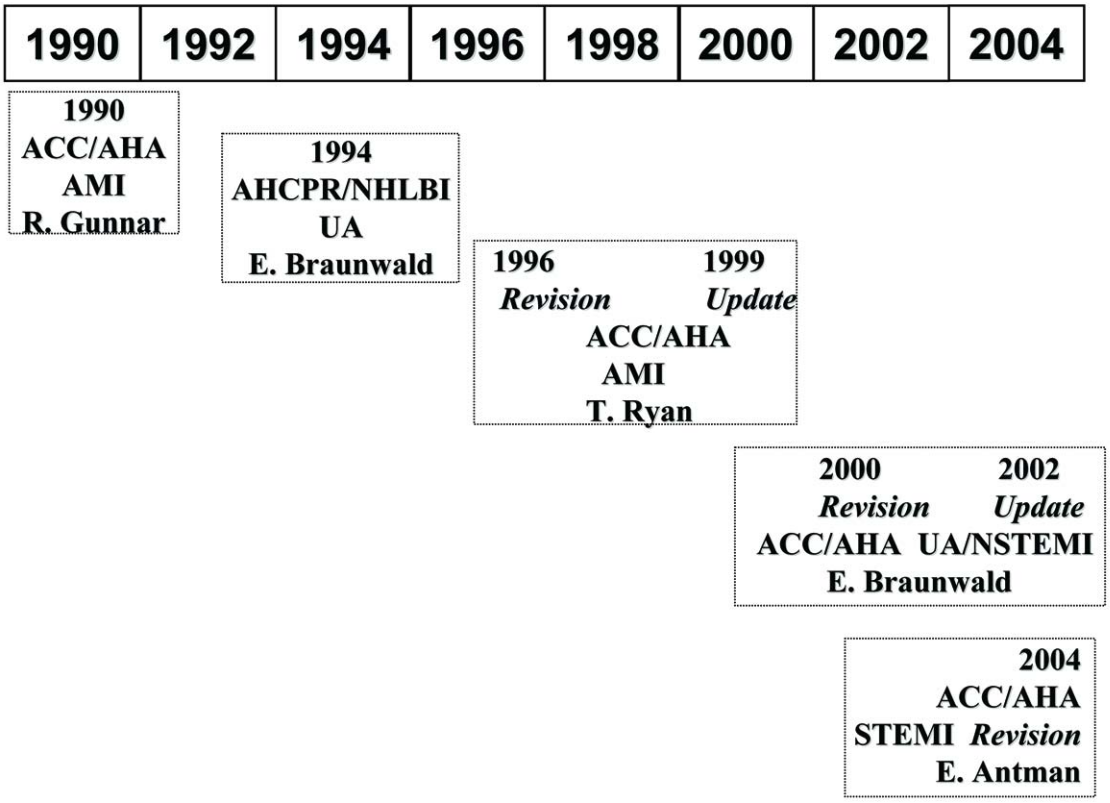

Figure 1. Evolution of ACC/AHA guidelines for management of patients with acute MI. The first guideline published by the ACC/AHA described the management of patients with acute myocardial infarction (AMI). The subsequent three documents were the Agency for Healthcare and Quality/National Heart, Lung and Blood Institute sponsored guideline on management of unstable angina (UA), the revised/updated ACC/AHA guideline on AMI, and the revised/updated ACC/AHA guideline on unstable angina/non–ST-segment myocardial infarction (UA/NSTEMI). The present guideline is a revision and deals strictly with the management of patients presenting with ST-elevation myocardial infarction (STEMI). The names of the chairs of the writing committees for each of the guidelines are shown at the bottom of each box.

with acute coronary syndromes, the ACC/AHA Task Force on Practice Guidelines convened a committee (also chaired by Dr. Braunwald) to revise the 1994 unstable angina guideline. That committee focused on patients presenting without ST elevation and introduced the nomenclature of unstable angina/non–ST-elevation MI (UA/NSTEMI). The "ACC/AHA Guidelines for the Management of Patients with UA/NSTEMI" were published in 2000 and were updated in electronic form in 2002 (4).

Although considerable improvement has occurred in the process of care for patients with ST-elevation MI (STEMI), room for improvement exists (5-7). The purpose of the present guideline is to focus on the numerous advances in the diagnosis and management of patients with STEMI since 1999. This is reflected in the changed name of the guideline: "ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction" (Figure 1). It is recognized that there are areas of overlap among this guideline on patients with STEMI, the guideline on patients with UA/NSTEMI, and other guidelines. The committee has handled this overlap by reiterating important concepts and recommendations in this guideline and by providing cross-references to other guidelines.

The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with STEMI summarize both clinical evidence and expert opinion. Once recommendations were written, a Classification of Recommendation and Level of Evidence grade was assigned to each recommendation. Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format as follows:

Classification of Recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

The schema for classification of recommendations and level of evidence is summarized in Table 1, 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.

The committee recognizes the importance of timely reperfusion for patients with STEMI and spent considerable effort reviewing the literature published since 1999 when formulating recommendations. Along with reperfusion by pharmacological and catheter-based means, the committee emphasized the use of established therapies such as aspirin, beta-adrenoceptor–blocking agents, vasodilator therapy, angiotensin converting enzyme (ACE) inhibitors, and cholesterol-lowering therapy. To provide clinicians with a set of recommendations that can easily be translated into the practice of caring for patients with STEMI, this guideline is organized around the chronology of the interface between the patient and the clinician (Figure 2) (8-10). Thus, readers will find material on prevention of STEMI, patient education, prehospital issues, initial recognition and management in the emergency department (ED), hospital management, and long-term management after treatment for the index STEMI event. The reorganization of the material in this guideline along the timeline noted above necessitated considerable modification of the sequence of text presented in the 1996 and 1999 guidelines on AMI. Whenever possible, the writing committee used the term STEMI rather than AMI. Given the reorganization of the guideline along the chronology of clinical care of patients with STEMI and the anticipated desire of readers to search the guideline for specific advice on management of patients with STEMI at different phases of their illness, in a few selected instances, recommendations and, to a lesser extent, some portions of the text are repeated.

Although these guidelines on STEMI have been shaped largely within the context of evidence-based medical practice, the committee clearly understands that variations in inclusion and exclusion criteria from one randomized trial to another impose some limitation on the generalizability of their findings. Likewise, in its efforts to reconcile conflicting data, the committee emphasized the importance of properly characterizing the population under study.

Writing committee members were selected with attention to cardiovascular subspecialties, broad geographical representation, and involvement in academic medicine and primary practice, including neurology, emergency medicine, and nursing. The Writing Committee on the Management of Patients with ST-Elevation Myocardial Infarction also included members of the ACCF Board of Governors, the American Academy of Family Physicians (AAFP), and the Canadian Cardiovascular Society (CCS).

Table 1. 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* *No additional studies needed* Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
Level A *Multiple (3-5) population risk strata 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 from multiple randomized trials or meta-analyses
Level B *Limited (2-3) population risk strata 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 strata evaluated**	• 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 †	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 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 the STEMI 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 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.

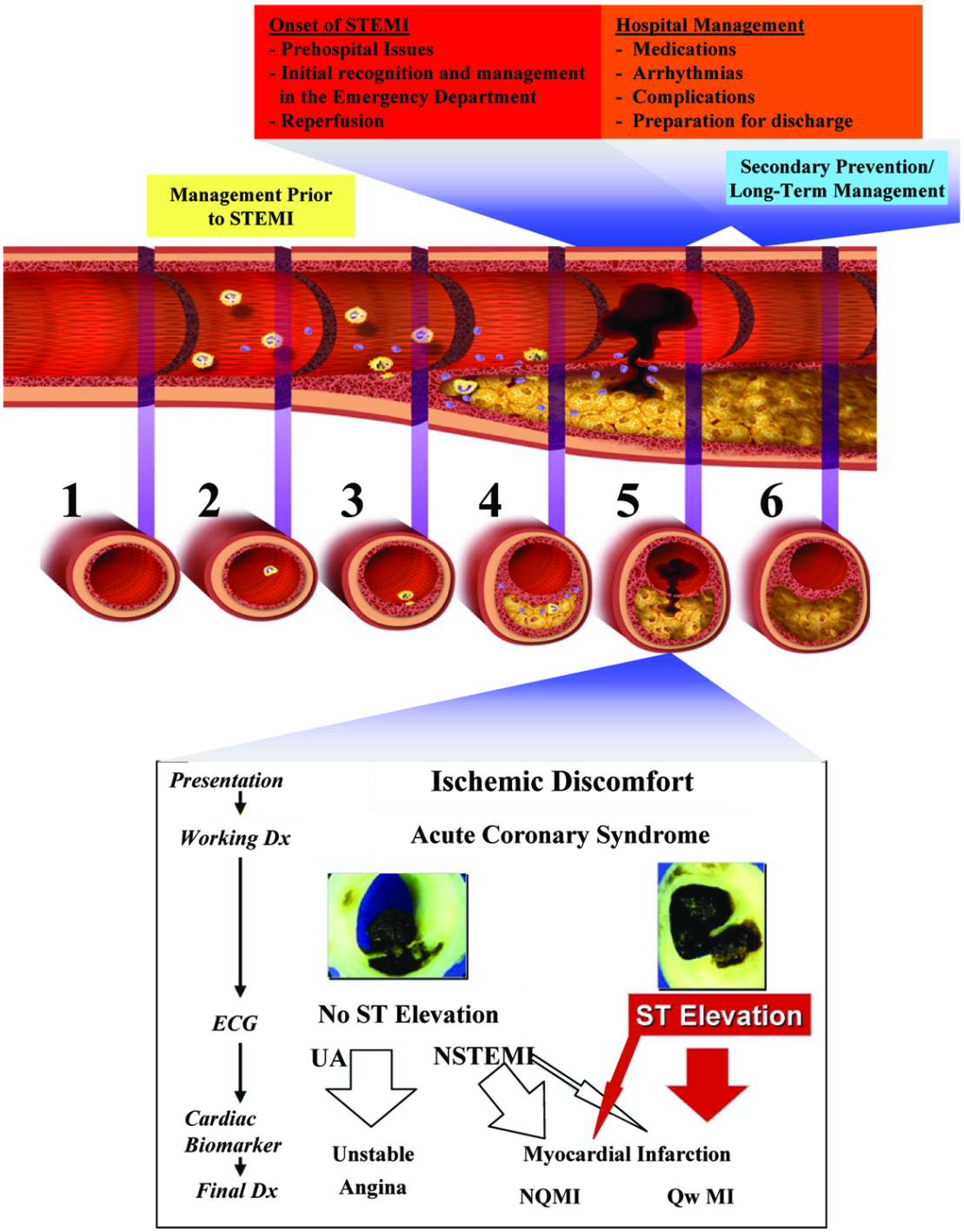

Figure 2. Acute coronary syndromes. The top half of the figure illustrates the chronology of the interface between the patient and the clinician through the progression of plaque formation, onset and complications of STEMI along with relevant management considerations at each stage. The longitudinal 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 CK-MB 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; CK-MB = MB isoenzyme of creatine kinase. Modified with permission from Libby. Circulation 2001;104:365-72 (8), Hamm, Bertrand, Braunwald. The Lancet 2001;358:1533-8 (9), and Davies. Heart 2000;83:361-6 (10) with permission from the BMJ Publishing Group.

The committee conducted comprehensive searching of the scientific and medical literature on AMI, with special emphasis on STEMI. Literature searching was limited to publications on humans and in English from 1990 to 2004. In addition to broad-based searching on MI, specific targeted searches were performed on MI and the following subtopics: 9-1-1, patient delays, emergency medical services (EMS), prehospital fibrinolysis, prehospital ECG, ED, supplemental oxygen, nitroglycerin, ASA, clopidogrel, arrhythmia, reperfusion, fibrinolysis/fibrinolytic therapy, angioplasty, stent, coronary artery bypass graft surgery (CABG), glycoprotein (GP) IIb/IIIa, pericarditis, beta-blockers, ischemia, intra-arterial pressure monitoring, ACE inhibitors, amiodarone, procainamide, lidocaine, electrical cardioversion, atropine, temporary pacing, transvenous pacing, permanent pacing, cardiac repair, heparin, low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), ramipril, calcium channel blockers, verapamil, nifedipine, magnesium, stress ECG, invasive strategy, secondary prevention, statins, and cholesterol. The complete list of keywords is beyond the scope of this section. The committee reviewed all compiled reports from computerized searches and conducted additional searching by hand. Literature citations were generally restricted to published manuscripts appearing in journals listed in Index Medicus. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts were cited when they were the only published information available.

This document was reviewed by 3 outside reviewers nominated by the ACC and 3 outside reviewers nominated by the AHA, as well as 1 reviewer each from the AAFP and the CCS, and 58 individual content reviewers. (See Appendix 2 for details.)

This document was approved for publication by the governing bodies of the American College of Cardiology Foundation and the American Heart Association and endorsed by the Canadian Cardiovascular Society. These guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are revised or withdrawn from distribution.

2. PATHOLOGY

2.1. Role of Acute Plaque Change

Slowly accruing high-grade stenoses of epicardial coronary arteries may progress to complete occlusion but do not usually precipitate STEMI, probably because of the development over time of a rich collateral network. However, during the natural evolution of atherosclerotic plaques, especially those that are lipid laden, an abrupt and catastrophic transition may occur, characterized by plaque disruption by rupture of the fibrous cap or erosion of the surface of the fibrous cap (Figure 2) (8-10). Plaques that are prone to disruption are usually nonobstructive, are characterized by abundant macrophages and other inflammatory cells, and are often located at branch points or bends in the arterial tree (11-15). They are referred to as vulnerable or high-risk plaques. After plaque disruption, there is exposure of substances that promote platelet activation, adhesion, and aggregation, thrombin generation, and ultimately thrombus formation (16,17). The resultant thrombus can completely occlude the epicardial infarct artery. If there is an insufficient collateral supply, a wave front of myocardial necrosis begins within 15 minutes and spreads from the endocardium toward the epicardium (18). This may be modulated by the extent of collateral flow and determinants of myocardial oxygen consumption, affording opportunity for significant myocardial salvage (19). Of note, intravascular ultrasound studies suggest that in addition to the disruptured plaque, several other vulnerable or high-risk plaques may coexist throughout the coronary vasculature.

2.2. Acute Coronary Syndromes

Disruption of vulnerable or high-risk plaques is the common pathophysiological substrate of the acute coronary syndromes that comprise a spectrum of myocardial ischemia. Patients with an acute coronary syndrome include those whose clinical presentations cover the following range of diagnoses: unstable angina, MI without ST elevation (NSTEMI), and MI with ST elevation (STEMI) (Figure 2) (8-10). Patients with STEMI have a high likelihood of a coronary thrombus occluding the infarct artery (20,21). Angiographic evidence of coronary thrombus formation may be seen in more than 90% of patients with STEMI but in only 1% of patients with stable angina and about 35% to 75% of patients with unstable angina or NSTEMI (20-24). However, not every STEMI evolves into a Q-wave MI; likewise, a patient with NSTEMI may develop Q waves. The acute coronary syndrome spectrum concept is a useful framework for developing therapeutic strategies. Antithrombin therapy and antiplatelet therapy should be administered to all patients with an acute coronary syndrome regardless of the presence or absence of ST-segment elevation. Patients presenting with persistent ST-segment elevation are candidates for reperfusion therapy (either pharmacological or catheter-based) to restore flow promptly in the occluded epicardial infarct-related artery and are the subject of this guideline (Figure 3) (24-40). Patients presenting without ST-segment elevation are not candidates for immediate pharmacological reperfusion but should receive anti-ischemic therapy and catheter-based therapy where applicable as discussed in the ACC/AHA Guidelines for Management of Patients with UA/NSTEMI (4).

2.3. Pathophysiology

A key concept in the pathophysiology of STEMI is ventricular remodeling, a term that refers to changes in size, shape, and thickness of the left ventricle involving both the infarcted and noninfarcted segments of the ventricle (41,42). Acute dilatation and thinning of the area of infarction that is not due to additional myocardial necrosis is referred to as infarct expansion (43). An extra load is placed on the residual functioning myocardium, which results in compensatory hypertrophy. Inhibition of the renin-angiotensin-aldosterone sys-

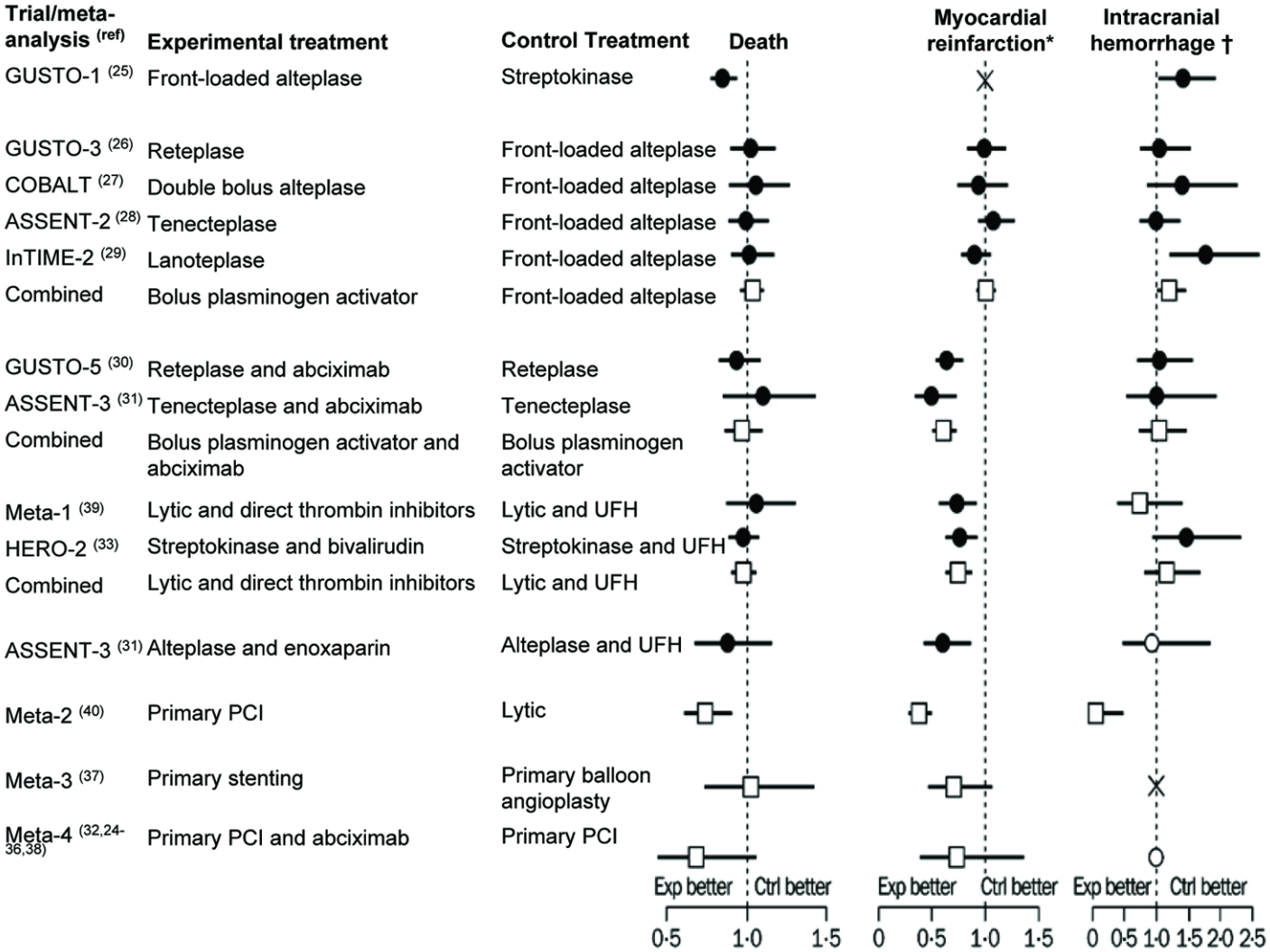

Figure 3. Relative treatment effect associated with several acute reperfusion modalities in patients presenting with STEMI. Data are odds ratios and 95% confidence intervals. UFH = unfractionated heparin; PCI = percutaneous coronary intervention; Exp = experimental group; Ctrl = control group. *Data for myocardial reinfarction as a single end point were not available for meta-3; in this case the figure presents odds ratios for the composite of death or myocardial reinfarction. †Intracranial hemorrhage was not reported in meta-1-data were derived from the HERO-1, HIT-4, TIMI9b, and GUSTO2b trials that were included in this meta-analysis. Modified with permission from Elsevier (Boersma et al. The Lancet 2003;361:847-58) (24).

tem is a key therapeutic maneuver in patients with STEMI (44). Additional important pathophysiological concepts in patients with STEMI that form the basis for recommendations in this guideline include cardiac arrhythmias such as those that result from electrical instability, pump failure/excessive sympathetic stimulation, and conduction disturbances. Mechanical problems that result from dysfunction or disruption of critical myocardial structures (e.g., mitral regurgitation [MR], rupture of the interventricular septum, ventricular aneurysm formation, and free wall rupture) may require a combination of pharmacological, catheter-based, and surgical treatments.

2.4. Epidemiology

STEMI continues to be a significant public health problem in industrialized countries and is becoming an increasingly significant problem in developing countries (45). Although the exact incidence is difficult to ascertain, using first-listed and secondary hospital discharge data, there were 1 680 000 unique discharges for ACS in 2001 (46). Applying the conservative estimate of 30% of the ACS patients who have STEMI from the National Registry of Myocardial Infarction [NRMI-4] (46a), we estimate 500 000 STEMI events per year in the U.S. However, there has been a steady decline in the mortality rate from STEMI over the last several decades. This appears to be due to a combination of a fall in the incidence of MI (replaced in part by an increase in the incidence of unstable angina) and a reduction in the case fatality rate once an MI has occurred (47-49). There has been a progressive increase in the proportion of patients who present with NSTEMI compared with STEMI.

The committee strongly endorses several public health campaigns that are likely to contribute to a reduction in the incidence of and fatality from STEMI in the future. These

include the following: 1) recognition of diabetes mellitus and chronic kidney disease as "risk equivalents" to coronary heart disease (CHD) and therefore recommendation for more aggressive attempts at control of other risk factors (50,51); 2) recognition of the importance of dyslipidemia as a major risk factor for CHD and recommendation for aggressive attempts at cholesterol reduction and treatment of the metabolic syndrome (50); 3) aggressive primary prevention efforts at smoking cessation as emphasized by the World Health Organization; 4) patient education campaigns regarding the signs and symptoms of MI and the appropriate courses of action to be taken (52,53); and 5) implementation at a professional level of quality assurance projects such as the ACC's "Guidelines Applied in Practice" (54) and the AHA's "Get with the Guidelines" (55) to improve compliance with established treatment strategies when caring for patients with MI. A proposal that holds great promise for reducing the morbidity and mortality associated with STEMI is the regionalization of care for patients with acute coronary syndromes using centers of excellence (56-58).

3. MANAGEMENT BEFORE STEMI

One third of patients who experience STEMI will die within 24 hours of the onset of ischemia, and many of the survivors will suffer significant morbidity (24). For many patients, the first manifestation of CHD will be sudden death. The major risk factors for development of CHD and STEMI are well established. Clinical trials have demonstrated that modification of those risk factors can prevent the development of CHD (primary prevention) or reduce the risk of experiencing STEMI in patients who have CHD (secondary prevention). All practitioners should emphasize prevention and refer patients to primary care providers for appropriate long-term preventive care. In addition to internists and family physicians, cardiologists have an important leadership role in primary (and secondary) prevention efforts.

3.1. 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 CHD for all patients at regular intervals (approximately every 3 to 5 years).** ***(Level of Evidence: C)***
2. **Ten-year risk (National Cholesterol Education Program [NCEP] global risk) of developing symptomatic CHD should be calculated for all patients who have 2 or more major risk factors to assess the need for primary prevention strategies (59).** ***(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)***

Major risk factors for developing CHD (i.e., smoking, family history, adverse lipid profiles, and elevated blood pressure) have been established from large long-term epidemiological studies (59,60). These risk factors are predictive for most populations in the United States. Primary prevention interventions aimed at these risk factors are effective when used properly. They can also be costly in terms of primary care physician time, diversion of attention from other competing and important healthcare needs, and expense, and they may not be effective unless targeted at higher-risk patients (61). It is therefore important for primary care providers to make identifying patients at risk, who are most likely to benefit from primary prevention, a routine part of everyone's health care. The Third Report of the NCEP provides guidance on identifying such patients (59).

Patients with 2 or more risk factors who are at increased 10-year risk will have the greatest benefit from primary prevention, but any individual with a single elevated risk factor is a candidate for primary prevention. Waiting until the patient develops multiple risk factors and increased 10-year risk contributes to the high prevalence of CHD in the United States (59,62). Such patients should have their risk specifically calculated, by any of the several available valid prognostic tools available in print (59,63), on the internet (64), or for use on a personal computer or PDA (Personal Digital Assistant) (59). Patients' specific risk levels determine the absolute risk reductions they can obtain from preventive interventions and guide selection and prioritization of those interventions. For example, target levels for lipid lowering and for antihypertensive therapy vary by patients' baseline risk. A specific risk number can also serve as a powerful educational intervention to motivate lifestyle changes (65).

3.2. Interventions to Reduce Risk of STEMI

The benefits of prevention of STEMI in patients with CHD are well documented and of large magnitude (62,66-68). 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 for high-risk primary prevention regardless of sex (69). Patients with diabetes and peripheral vascular disease have baseline risks of STEMI similar to patients with known CHD, as do patients with multiple risk factors predicting calculated risk of greater than 20% over 10 years as estimated by the Framingham equations (59). Such patients should be considered to have the risk equivalents of CHD, and they can be expected to have an absolute benefit similar to those with established CHD.

All patients who smoke should be encouraged to quit and should be provided with help in quitting at every opportunity. Even a single recommendation by a clinician to quit smoking can have a meaningful impact on the rate of cessation of smoking. The most effective strategies for encouraging quitting are those that identify patients' level or stage of readiness and provide information, support, and, if necessary,

pharmacotherapy targeted at the individual's readiness and specific needs (66,70). Pharmacotherapy may include nicotine replacement or withdrawal-relieving medication such as bupropion. Most patients require several attempts before succeeding in quitting permanently. Additional discussion in this area can be found in the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina (71).

All patients should be instructed in and encouraged to maintain appropriate low-saturated-fat and low-cholesterol diets high in soluble (viscous) fiber and rich in vegetables, fruits, and whole grains. The statin drugs have the best outcome evidence supporting their use and should be the mainstay of pharmacological intervention (62). The appropriate levels for lipid management are dependent on baseline risk; the reader is referred to the NCEP report for details (59).

Primary prevention patients with high blood pressure should be treated according to the recommendations of the Seventh Joint National Committee on High Blood Pressure (JNC-7) (72,73). Specific treatment recommendations are based on the level of hypertension and the patient's other risk factors. A diet low in salt and rich in vegetables, fruits, and low-fat dairy products should be encouraged for all hypertensive patients, as should a regular aerobic exercise program. Most patients will require more than 1 medication to achieve blood pressure control, and pharmacotherapy should begin with known outcome-improving medications (primarily thiazide diuretics as first choice, with the addition of beta-blockers, ACE inhibitors, angiotensin receptor blockers, and long-acting calcium channel blockers) (72,74). Systolic hypertension is a powerful predictor of adverse outcome, particularly among the elderly, and should be treated even if diastolic pressures are normal (75).

Aspirin prophylaxis can uncommonly result in hemorrhagic complications and should only be used in primary prevention when the level of risk justifies it. Patients whose 10-year risk of CHD is 6% or more are most likely to benefit, and aspirin 75 to 162 mg/d as primary prophylaxis should be discussed with such patients (76-79).

3.3. Patient Education for Early Recognition and Response to STEMI

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, including the phone number to access EMS, generally 9-1-1 (80) *(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 1 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)***

Morbidity and mortality from STEMI can be reduced significantly if patients and bystanders recognize symptoms early, activate the EMS system, and thereby shorten the time to definitive treatment. Patients with possible symptoms of STEMI should be transported to the hospital by ambulance rather than by friends or relatives, because there is a significant association between arrival at the ED by ambulance and early reperfusion therapy (81-84). In addition, emergency medical technicians (EMTs) and paramedics can provide life-saving interventions (e.g., early cardiopulmonary resuscitation [CPR] and defibrillation) if the patient develops cardiac arrest. Approximately 1 in every 300 patients with chest pain transported to the ED by private vehicle goes into cardiac arrest en route (85).

Several studies have confirmed that patients with STEMI usually do not call 9-1-1 and are not transported to the hospital by ambulance. A follow-up survey of chest pain patients presenting to participating EDs in 20 US communities who were either released or admitted to the hospital with a confirmed coronary event revealed that the average proportion of patients who used EMS was 23%, with significant geographic difference (range 10% to 48%). Most patients were driven by someone else (60%) or drove themselves to the hospital (16%) (86). In the National Registry of Myocardial Infarction 2, just over half (53%) of patients with STEMI were transported to the hospital by ambulance (82).

Even in areas of the country that have undertaken substantial public education on warning signs of STEMI and the need to activate the EMS system rapidly, either there were no increases in EMS use (87-91) or EMS use increased (as a secondary outcome measure) but was still suboptimal, with a 20% increase from a baseline of 33% in all 20 communities in the Rapid Early Action for Coronary Treatment (REACT) study (92) and an increase from 27% to 41% in southern Minnesota after a community campaign (93). Given the importance of patients using EMS for possible acute cardiac symptoms, communities, including medical providers, EMS systems, healthcare insurers, hospitals, and policy makers at the state and local level, need to have agreed-upon emergency protocols to ensure patients with possible heart attack symptoms will be able to access 9-1-1 without barriers, to secure their timely evaluation and treatment (94).

As part of making a plan with the patient for timely recognition and response to an acute event, providers should review instructions for taking nitroglycerin in response to chest discomfort/pain. If a patient has previously been prescribed nitroglycerin, it is recommended that the patient be advised to take ONE nitroglycerin dose sublingually promptly for chest discomfort/pain. If symptoms are unimproved or worsening 5 minutes after ONE nitroglycerin dose has been taken, it is also recommended that the patient be instructed to call 9-1-1 immediately to access EMS. Although the traditional recommendation is for patients to take 1 nitroglycerin dose sublingually, 5 minutes apart, for up to 3 doses before calling for emergency evaluation, this recommendation has been modified by the writing committee to encourage earlier contacting of EMS by patients with symptoms suggestive of STEMI. Self-treatment with prescription medication, including nitrates, and with nonprescription medication (e.g., antacids) has been documented as a frequent cause of delay among patients with STEMI, including those with a history of MI or angina (95,96). Both the rate of use of these medications and the number of doses taken were positively correlated with delay time to hospital arrival (95).

Family members, close friends, or advocates should be included in these discussions and enlisted as reinforcement for rapid action when the patient experiences symptoms of a possible STEMI (3,80,97) (Figure 4). For patients known to their providers to have frequent angina, physicians may consider a selected, more tailored message that takes into account the frequency and character of the patient's angina and their typical time course of response to nitroglycerin. Avoidance of patient delay associated with self-medication and prolonged re-evaluation of symptoms is paramount.

Taking an aspirin in response to acute symptoms by patients has been reported to be associated with a delay in calling EMS (86). Patients should focus on calling 9-1-1, which activates the EMS system, where they may receive instructions from emergency medical dispatchers to chew aspirin (162 to 325 mg) while emergency personnel are en route, or emergency personnel can give an aspirin while transporting the patient to the hospital (98). Alternatively, patients may receive an aspirin as part of their early treatment once they arrive at the hospital if it has not been given in the prehospital setting (3).

Providers should target those patients at increased risk for STEMI, focusing on patients with known CHD, peripheral vascular disease, or cerebral vascular disease, those with diabetes, and patients with 10-year Framingham risk of CHD of greater than 20% (99). They should stress that the chest discomfort will usually not be dramatic, such as is commonly misrepresented on television or in the movies as a "Hollywood heart attack." Providers should also describe anginal equivalents and the commonly associated symptoms of STEMI (e.g., shortness of breath, a cold sweat, nausea, or lightheadedness) in both men and women (83), as well as the increased frequency of atypical symptoms in elderly patients (100).

In September 2001, the NHAAP and the AHA launched a campaign urging patients and providers to "Act in Time to Heart Attack Signs" (101). The campaign urges both men and women who feel heart attack symptoms or observe the signs in others to wait no more than a few minutes, 5 minutes at most, before calling 9-1-1 (101,102). Campaign materials point out that patients can increase their chance of surviving a STEMI by learning the symptoms and filling out a survival plan. They also are advised to talk with their doctor about heart attack and how to reduce their risk of having one. The patient materials include a free brochure about symptoms and recommended actions for survival, in English (103) and Spanish (104), as well as a free wallet card that can be filled in with emergency medical information (105). Materials geared directly to providers include a Patient Action Plan Tablet (106), which contains the heart attack warning symptoms and steps for developing a survival plan individualized with the patient's name; a quick reference card for addressing common patient questions about seeking early treatment to survive a heart attack (107), including a palm pilot version (108); and a warning signs wall chart (109). These materials and others are available on the "Act in Time" Web page (www.nhlbi.nih.gov/actintime) (51,101) (Figure 5).

4. ONSET OF STEMI

4.1. Recognition of Symptoms by Patient

Early recognition of symptoms of STEMI by the patient or someone with the patient is the first step that must occur before evaluation and life-saving treatment can be obtained. Although many lay persons are generally aware that chest pain is a presenting symptom of STEMI, they are unaware of the common associated symptoms, such as arm pain, lower jaw pain, shortness of breath, and diaphoresis (111) or anginal equivalents. The average patient with STEMI does not seek medical care for approximately 2 hours after symptom onset, and this pattern appears unchanged over the last decade (45,87,112). Average and median delays for patients with STEMI were 4.7 and 2.3 hours, respectively, from the 14-country Global Registry of Acute Coronary Events (GRACE) project. Approximately 41% of patients with STEMI presented to the 94 study hospitals within 2 hours of acute cardiac ischemia symptom onset (113).

A baseline analysis from the REACT research program demonstrated longer delay times among non-Hispanic blacks, older patients, and Medicaid-only recipients and shorter delay times among Medicare recipients (compared with privately insured patients) and among patients who came to the hospital by ambulance (87). In the majority of studies examined to date, women in both univariate and multivariate adjusted analyses (in which age and other potentially confounding variables have been controlled) exhibit more prolonged delay patterns than men (113).

A number of studies have provided insight into why patients delay in seeking early care for heart symptoms (Table 2) (114). Focus groups conducted for the REACT research program (92,115) revealed that patients commonly

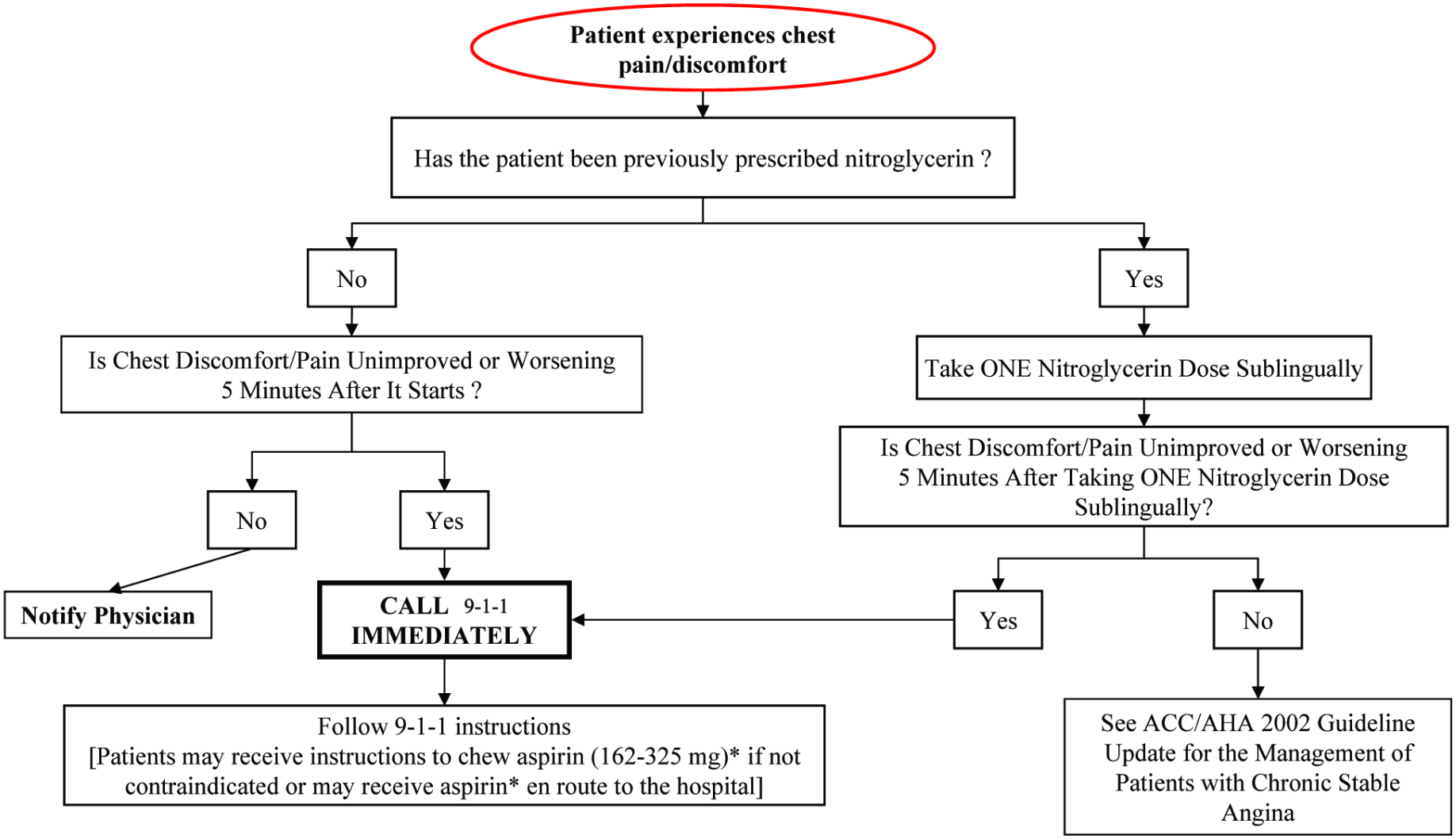

Figure 4. Patient (advance) instructions for nitroglycerin use and EMS contact in the setting of non–trauma-related chest discomfort/pain. Treatment algorithm for potential patients with STEMI who experience non–trauma-related chest discomfort/pain. If patients experience chest discomfort/pain, and have been previously prescribed nitroglycerin (NTG) and have it available (right side of algorithm), it is recommended that they be instructed (in advance) to take ONE NTG dose sublingually immediately in response to symptoms. If chest discomfort/pain is unimproved or worsening 5 minutes after taking ONE NTG dose sublingually, it is recommended that the patient call 9-1-1 immediately to access EMS. If the symptoms disappear after taking ONE NTG dose, the angina management recommendations in the ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina apply. If patients are not previously prescribed NTG (left side of algorithm), it is recommended that they call 9-1-1 if chest discomfort/pain is unimproved or worsening 5 minutes after it starts. If the symptoms subside within 5 minutes of when they began, patients should notify their physician of the episode. [For those patients with new onset chest discomfort who have not been prescribed nitroglycerin, it is appropriate to discourage them from seeking someone else's nitroglycerin (e.g., from a neighbor, friend, or relative).] *Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations.

Figure 5. Act in Time to Heart Attack Signs

Use the T.I.M.E. Method To Help Your Patients Make a Heart Attack Survival Plan

Why Your Patients Need To Act in Time to Heart Attack Signs

Coronary heart disease is the leading killer of both men and women in the United States. Each year, about 1.1 million Americans suffer a heart attack. About 460,000 of those heart attacks are fatal. Disability and death from heart attack can be reduced with prompt thrombolytic and other artery-opening therapies–ideally given within the first hour after symptom onset. Patient delay is the largest barrier to receiving therapy quickly.

Heart Attack Warning Signs

- **Chest discomfort** (pressure, squeezing, fullness, or pain in the center of the chest)
- **Discomfort in one or both arms, back, neck, jaw, or stomach**
- **Shortness of breath** (often comes with or before chest discomfort)
- **Breaking out in a cold sweat, nausea, or light-headedness**

Uncertainty Is Normal

Most people think a heart attack is sudden and intense, like a "movie heart attack." The fact is that many heart attacks start slowly as mild pain or discomfort. People who feel such symptoms may not be sure what is wrong.

Delay Can Be Deadly

Most heart attack victims wait 2 or more hours after symptoms begin before they seek medical help. People often take a wait-and-see approach or deny that their symptoms are serious. Every minute that passes without treatment means that more heart muscle dies.

Calling 9-1-1 Saves Lives

Minutes matter. Anyone with heart attack symptoms ***should not wait more than a few minutes–5 minutes at most–to call 9-1-1.***

From: Act in Time to Heart Attack Signs. Action Plan. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. National Heart, Lung, and Blood Institute. NIH Publication No. 01-3313, September 2001 http://nhlbi.nih.gov/health/prof/heart/mi/provider.pdf (110)

Use the T.I.M.E. Method:

Talk with your patients about—

- Risk of a heart attack.
- Recognition of symptoms.
- Right action steps to take/rationale for rapid action.
- Rx–give instructions for when symptoms occur (based on patient history).
- Remembering to call 9-1-1 quickly–within 5 minutes.

Investigate—

- Feelings about heart attack.
- Barriers to symptom evaluation and response.
- Personal and family experience with AMI and emergency medical treatment.

Make a plan—

- Help patients and their family members to make a plan for exactly what to do in case of heart attack symptoms.
- Encourage patients and their family members to rehearse the plan.

Evaluate—

- The patient's understanding of risk in delaying.
- The patient's understanding of your recommendations.
- The family's understanding of risk and their plan for action.

Additional Resources

Find information and educational materials at the National Heart, Lung, and Blood Institute Web site: www.nhlbi.nih.gov and the American Heart Association Web site: www.americanheart.org

NATIONAL INSTITUTES OF HEALTH
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Table 2. Reasons Patients Delay Seeking Medical Attention for Symptoms of ST-Elevation Myocardial Infarction

Expected a dramatic presentation
Thought symptoms were not serious/would go away
Took a "wait and see" approach to the initial symptoms that included self-evaluation, self-treatment, and reassessment until "certain"
Tended to attribute symptoms to other chronic conditions (e.g., arthritis, muscle strain) or common illnesses (e.g., influenza)
Lacked awareness of the benefits of rapid action, reperfusion treatment, or of the importance of calling EMS/9-1-1 for acute MI symptoms
Expressed fear of embarrassment if symptoms turned out to be a false alarm; reluctant to "bother" physicians or EMS unless "really sick"; need "permission" from others such as healthcare providers, spouses, family to take rapid action
Few ever discussed symptoms, responses, or actions for a heart attack in advance with family or providers
Stereotypes of who is at risk for a heart attack
Not perceived at risk if:
Young and healthy (especially men)
A woman
Under a doctor's care or making lifestyle changes (especially men with risk factors)

Based on findings from Finnegan et al. Preventive Medicine 2000;31:205-13 (114).

hold a pre-existing expectation that a heart attack would present dramatically with severe, crushing chest pain, such that there would be no doubt that one was occurring. This was in contrast to their actual reported symptom experience of a gradual onset of discomfort involving midsternal chest pressure or tightness, with other associated symptoms often increasing in intensity. The ambiguity of these symptoms, due to this disconnect between prior expectations and actual experience, resulted in uncertainty about the origin of symptoms and thus a "wait-and-see" posture by patients and those around them (114). Other reported reasons for delay were that patients thought the symptoms were self-limited and would go away or were not serious (95,116,117); that they attributed symptoms to other pre-existing chronic conditions, especially among the elderly with multiple chronic conditions (e.g., arthritis), or sometimes to a common illness such as influenza; that they were afraid of being embarrassed if symptoms turned out to be a "false alarm"; that they were reluctant to trouble others (e.g., providers, EMS) unless they were "really sick" (95,116,117); that they held stereotypes of who is at risk for a heart attack; and that they lacked awareness of the importance of rapid action, knowledge of reperfusion treatment, or knowledge of the benefits of calling EMS/9-1-1 to ensure earlier treatment (Table 2) (Figure 5) (51,114) . Notably, women did not perceive themselves to be at risk (53).

4.1.1. Silent and Unrecognized Events

Patients experiencing STEMI do not always present with chest discomfort (118). The Framingham Study was the first to show that as many as half of all MIs may be clinically silent and unrecognized by the patient (119). Canto et al. (100) found that one third of the 434 877 patients with confirmed MI in the National Registry of Myocardial Infarction (NRMI) (100) presented to the hospital with symptoms other than chest discomfort. Compared with MI patients with chest discomfort, MI patients without chest discomfort were more likely to be older (74.2 versus 66.9 years), women (49.0% versus 38.0%), diabetic (32.6% versus 25.4%), and/or have prior heart failure (26.4% versus 12.3%). MI patients without chest discomfort delayed longer before they went to the hospital (mean 7.9 versus 5.3 hours) and were less likely to be diagnosed as having an MI when admitted (22.2% versus 50.3%). They also were less likely to receive fibrinolysis or primary percutaneous coronary intervention (PCI) (25.3% versus 74.0%), aspirin (60.4% versus 84.5%), beta-blockers (28.0% versus 48.0%), or heparin (53.4% versus 83.2%). Silent MI patients were 2.2 times (95% confidence interval [CI] 2.17 to 2.26) more likely to die during the hospitalization (in-hospital mortality rate 23.3% versus 9.3%). Healthcare providers should maintain a high index of suspicion for MI when evaluating women, diabetics, older patients, and those with a history of heart failure, as well as those patients complaining of chest discomfort but who have a permanent pacemaker that may confound recognition of STEMI on their 12-lead ECG (120).

4.2. 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 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)***

The majority of deaths from STEMI occur within the first 1 to 2 hours after symptom onset, usually from ventricular fibrillation (VF). Survival from VF is inversely related to the time interval between its onset and termination. For each minute that a patient remains in VF, the odds of survival decrease by 7% to 10% (121). Survival is optimal when both CPR and ACLS, including defibrillation and drug therapy, are provided early.

The AHA has introduced the "chain of survival" concept to represent a sequence of events that ideally should occur to maximize the odds of successful resuscitation from cardiac arrest (121). The links in the chain include early access (recognition of the problem and activation of the EMS sys-

tem by a bystander), early CPR, early defibrillation for patients who need it, and early ACLS.

Although estimates of overall survival from out-of-hospital cardiac arrest in the United States are as low as 5%, survival in patients who are in VF initially can be much higher. The percentage of patients who are found in VF and the likelihood of survival are higher if the patient's collapse is witnessed, bystander CPR is performed, and a monitor/defibrillator can be applied quickly. For example, 27% of patients with witnessed out-of-hospital cardiac arrest in Seattle, WA, survived to leave the hospital when bystanders performed CPR (122). Only 13% survived without bystander CPR. Emerging data suggest that treatment of VF with immediate defibrillation, irrespective of "down time," may not be optimal for all patients and that as the duration of cardiac arrest increases, different interventions may take priority over defibrillation, such as a period of chest compressions (with associated tissue oxygen delivery) after 3 minutes of VF before defibrillation (123).

There is often a long delay from the recognition of cardiac arrest to defibrillation in rural areas where travel time is long and in densely populated urban areas. Survival rates are often extremely low in such settings (124-126). In Seattle, WA, the majority of out-of-hospital cardiac arrest victims receive defibrillation within 5 to 7 minutes after the recognition of out-of-hospital cardiac arrest. In Rochester, MN, the addition of a police defibrillation program to conventional EMS services resulted in a median time to first shock of 5.9 minutes for patients in VF and a 49% rate of survival to discharge (127). Total cumulative survival experience at 7 years in this community was 40% (128). Outcomes data on all Rochester, MN, patients who had an out-of-hospital cardiac arrest with VF from 1990 to 2000 who received defibrillation from emergency personnel showed that 72% survived to hospital admission and 40% were neurologically intact at discharge, with a mean follow-up of 4.8 years (129).

The key to improved survival appears to be the availability of early defibrillation. In the Ontario Pre-hospital Advanced Life Support (OPALS) study, which involved 19 suburban and urban communities, improving the proportion of out-of-hospital cardiac arrest patients who were reached by a defibrillation-equipped ambulance within 8 minutes from 77% to 93% increased survival to hospital discharge from 3.9% to 5.2% (130). A 2-year prospective study at 3 Chicago, IL, airports of readily accessible AEDs in well-marked areas of the airport reported successful resuscitation in 11 of 18 patients with VF. Ten of the 18 were alive and neurologically intact at 1 year of follow-up (131).

Family members of patients with STEMI should be referred to a CPR program that combines CPR training with social support (132,133) (see Section 7.12.1). One study of the impact of in-home defibrillators on post-MI patients and their significant others reported that AEDs were valued by the participants and increased their perception of control over their heart disease, notably for those who believed their risk of cardiac arrest to be high (134). Research is under way to test the safety and effectiveness of home use of AEDs by family members of patients after MI (135).

5. PREHOSPITAL ISSUES

5.1. 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 non–public 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)***

EMS systems vary considerably among communities in their ability to evaluate and treat suspected patients with STEMI, with some providing little beyond first aid and early defibrillation, whereas others have highly trained paramedics with sophisticated technology and advanced protocols.

EMS systems have 3 traditional components: emergency medical dispatch, first response, and EMS ambulance response.

Emergency Medical Dispatch. Early access to EMS is promoted by a 9-1-1 system currently available to more than 90% of the United States population. Enhanced 9-1-1 systems provide the caller's location to the dispatcher, which permits rapid dispatch of prehospital personnel to locations even if the caller is not capable of verbalizing or the dispatcher cannot understand the location of the emergency. A major challenge is the widespread proliferation and use of cell phones. Current cell phone technology does not provide the location of the caller to an enhanced 9-1-1 center. Instead, such calls are usually answered by the state police, who then attempt to determine the location of the emergency and forward the call to the appropriate 9-1-1 center. Such additional steps often result in substantial delays in the dispatch of emergency units to the scene. Several technological solutions to this problem exist but have not yet been implemented by the cell phone industry. EMS healthcare workers should encourage enhanced cell phone technology to identify caller location on 9-1-1 systems.

In most communities, law enforcement or public safety officials are responsible for operating 9-1-1 centers, because in most locations, 85% of calls are for police assistance, 10% are for EMS, and 5% are for fire-related emergencies. Dispatchers who staff 9-1-1 centers typically have only minimal medical background and training and usually operate by following written cards and protocols that in many cases are

designed and updated locally. High-performance centers employ EMTs and/or paramedics who are specially trained and certified as emergency medical dispatchers. They, too, operate under written protocols, but such protocols are usually developed and upgraded at the national level. Such centers typically have intense quality-assurance programs to ensure that emergency medical dispatchers follow protocols and procedures correctly and consistently. This is particularly true for the prearrival instructions that are given to cardiac arrest bystanders to instruct them on how to perform CPR while awaiting arrival of emergency personnel (phone CPR) (136). Efforts to shorten the time for contact of the STEMI patient with the medical system are likely to require expansion of the number of trained emergency response personnel and consideration of streamlining methods for distinguishing emergency calls for medical assistance from other emergencies using separate phone numbers, as is the practice currently in some European countries.

First Response. To minimize time to treatment, particularly for cardiopulmonary arrest, many communities allow volunteer and/or paid firefighters and other first-aid providers to function as first responders, providing CPR and, increasingly, early defibrillation using AEDs until EMTs and paramedics arrive. AEDs have been shown to be safe and effective when used by trained first responders with a duty to act (137-139). Systems that incorporate AEDs to shorten response times are highly desirable. Ideally, there should be a sufficient number of trained personnel so that a trained first responder can be at the victim's side within 5 minutes of the call.

Another popular community approach to increase the number of out-of-hospital VF patients who receive early defibrillation is public access defibrillation (PAD), so named because the intent is to have laypersons perform early defibrillation. Experience thus far has been favorable in terms of efficacy and safety when trained public safety laypersons (e.g., flight attendants or security officers) have been allowed to use AEDs to treat cardiac arrest victims (131,140,141). Provision of early defibrillation with AEDs by non–public safety first responders is a promising new strategy to prevent sudden cardiac death after the onset of STEMI, but further study is needed to determine its safety and efficacy (142-147) (Ornato JP; oral presentation, American Heart Association 2003 Annual Scientific Sessions, November 2003, Orlando, FL).

EMS Ambulance Response. Most cities and larger suburban areas provide EMS ambulance services with providers from the fire department, a private ambulance company, and/or volunteers. The most common pattern is a tiered system in which some of the ambulances are staffed and equipped at the basic EMT level (which includes first aid and early defibrillation with AEDs) and other units (either transporting or nontransporting) are staffed by paramedics or other intermediate-level EMTs (who can, in addition to basic care, start intravenous [IV] drips, intubate, and administer medications). In some systems, the advanced providers can also perform 12-lead ECGs, provide external pacing for symptomatic bradycardia, and utilize other techniques. Some high-performance EMS systems have only advanced life support–staffed ambulances (all-ALS systems). Advantages of such systems are that they provide a uniform standard of care and, surprisingly, can actually lower cost by eliminating the need to dispatch 2 units in response to calls in which it is not clear to dispatchers initially that the patient needs advanced life support (149). The potential disadvantage of such models is that they typically have a relatively large number of paramedics, each of whom gets to perform their advanced skills less frequently than the smaller number of paramedics typically found in tiered systems (150).

Rural areas typically provide primarily basic life support ambulance services, usually by volunteers supplemented by a relatively small number of ALS units. In some cases, ALS is provided by paramedics or helicopter personnel who respond to the scene in addition to the basic life support ambulance.

5.2. 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 the 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 ECGs routinely on chest pain patients suspected of STEMI. *(Level of Evidence: B)***
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)***

Because the potential benefits of early aspirin use are great and the risks and costs are low, it is reasonable for physicians to encourage the prehospital administration of aspirin via EMS personnel (i.e., EMS dispatchers and providers) to patients with symptoms suggestive of STEMI unless its use is contraindicated (151). The AHA chest pain algorithm can be adapted for use by prehospital emergency personnel. This

protocol recommends empirical treatment of patients with suspected STEMI with Morphine, Oxygen, Nitroglycerin, and Aspirin (MONA) (102). Although short-acting nitroglycerin is often administered for temporary symptomatic relief, it can precipitate hypotension (especially if right ventricular [RV] infarction is present), and long-term nitrates have not been shown to decrease mortality in patients with STEMI (152). To facilitate earlier aspirin administration, it is reasonable that 9-1-1 dispatchers advise non–aspirin-allergic patients with symptoms of STEMI to chew 162 to 325 mg of aspirin while awaiting arrival of prehospital EMS providers. In the absence of instructions by emergency medical dispatchers, prehospital EMS providers (under medical direction) should administer an aspirin en route to the hospital as noted above. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations.

The AHA (102), the 31st Bethesda Conference of the American College of Cardiology (153), and a technology review supported by the NHLBI's NHAAP (154) strongly encourage the use of 12-lead ECGs by paramedics to evaluate all patients with chest discomfort suspected to be of ischemic origin in the prehospital setting (Figure 6) (Table 3) (155). This requires providing training and 12-lead ECG equipment to all ACLS personnel.

For patients who have ECG evidence of STEMI, it is reasonable that paramedics review a reperfusion checklist and relay the ECG and checklist findings to a predetermined medical control facility and/or receiving hospital (Table 3). The checklist should be designed to determine the presence or absence of comorbid conditions and underlying conditions in which fibrinolytic therapy may be hazardous. The checklist should also facilitate detection of patients with suspected STEMI who are at especially high risk (see Table 3), including those with severe heart failure or cardiogenic shock, for whom primary PCI is generally the preferred reperfusion strategy. (See Section 6.3.1.6.4.2.)

Active involvement of local healthcare providers, particularly cardiologists and emergency physicians, is needed to formulate local EMS protocols for patients with suspected STEMI, provide training, and secure equipment. In the future, regional centers of excellence for care of patients with STEMI may facilitate improvement of EMS protocols (56-58).

5.3. Prehospital Fibrinolysis

Class IIa

Establishment of a prehospital fibrinolysis protocol is reasonable in 1) settings in which physicians are present in the ambulance or 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, on-line medical command, a medical director with training/experience in STEMI management, and an ongoing continuous quality-improvement program. *(Level of Evidence: B)*

The selection of reperfusion strategy is discussed in Section 6.3.1.6.2 and involves assessment of the time from onset of symptoms, risk of STEMI, risk of bleeding, and the time required for transport to a skilled PCI lab. This section discusses issues related to prehospital fibrinolysis, which may bear on the timing and selection of reperfusion therapy.

Randomized controlled trials of fibrinolytic therapy have demonstrated the benefit of initiating fibrinolytic therapy as early as possible after onset of ischemic-type chest discomfort (155-157) (Figure 6). It seems reasonable to expect that if fibrinolytic therapy could be started at the time of prehospital evaluation, a greater number of lives could be saved. In Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3, 53% of patients received prehospital fibrinolysis within 2 hours after symptom onset (158). The value of reducing delay until treatment depends not only on the amount of time saved but also on when it occurs. Available data suggest that time saved within the first 1 to 2 hours has greater biological importance than time saved during the later stages of STEMI (156,157,159-164). Several randomized trials of prehospital-initiated fibrinolysis have advanced our understanding of the impact of early treatment (Table 4) (159,165-174). Acquisition of 12-lead ECGs in the field and use of a reperfusion checklist (Table 3) lead to more rapid prehospital and hospital care (159,175). Although none of the individual trials showed a reduction in mortality with prehospital-initiated fibrinolytic therapy, a meta-analysis of all available trials (before the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial [CAPTIM], which was performed after the meta-analysis) (173) demonstrated a 17% relative improvement in outcome associated with prehospital fibrinolytic therapy compared with in-hospital fibrinolytic therapy (95% CI 2% to 29%) (171). In the CAPTIM trial, patients randomized less than 2 hours after symptom onset had a strong trend toward lower 30-day mortality with prehospital fibrinolysis than did those randomized to primary PCI (2.2% versus 5.7%, p equals 0.058) (176). Similarly, patients in PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE-2) who were randomized within 3 hours of symptom onset (n equals 551) had no difference in mortality whether treated by fibrinolysis (7.4%) or transferred for PCI (7.3%) (177). Systems that have extensive experience with prehospital fibrinolysis with physician attendance in the ambulance and a well-integrated mechanism for obtaining and transmitting a 12-lead ECG continue to show excellent short- and long-term mortality results with prehospital fibrinolysis. Using data from a national registry, investigators in France reported 1-year mortality from STEMI of 6% in patients receiving prehospital fibrinolysis compared with 11% in patients receiving in-hospital fibrinolysis or primary PCI; the survival difference in favor of prehospital fibrinolysis persisted after adjustment for baseline characteristics (Danchin N; oral presentation, American Heart Association 2003 Annual Scientific Sessions, November 2003, Orlando, FL).

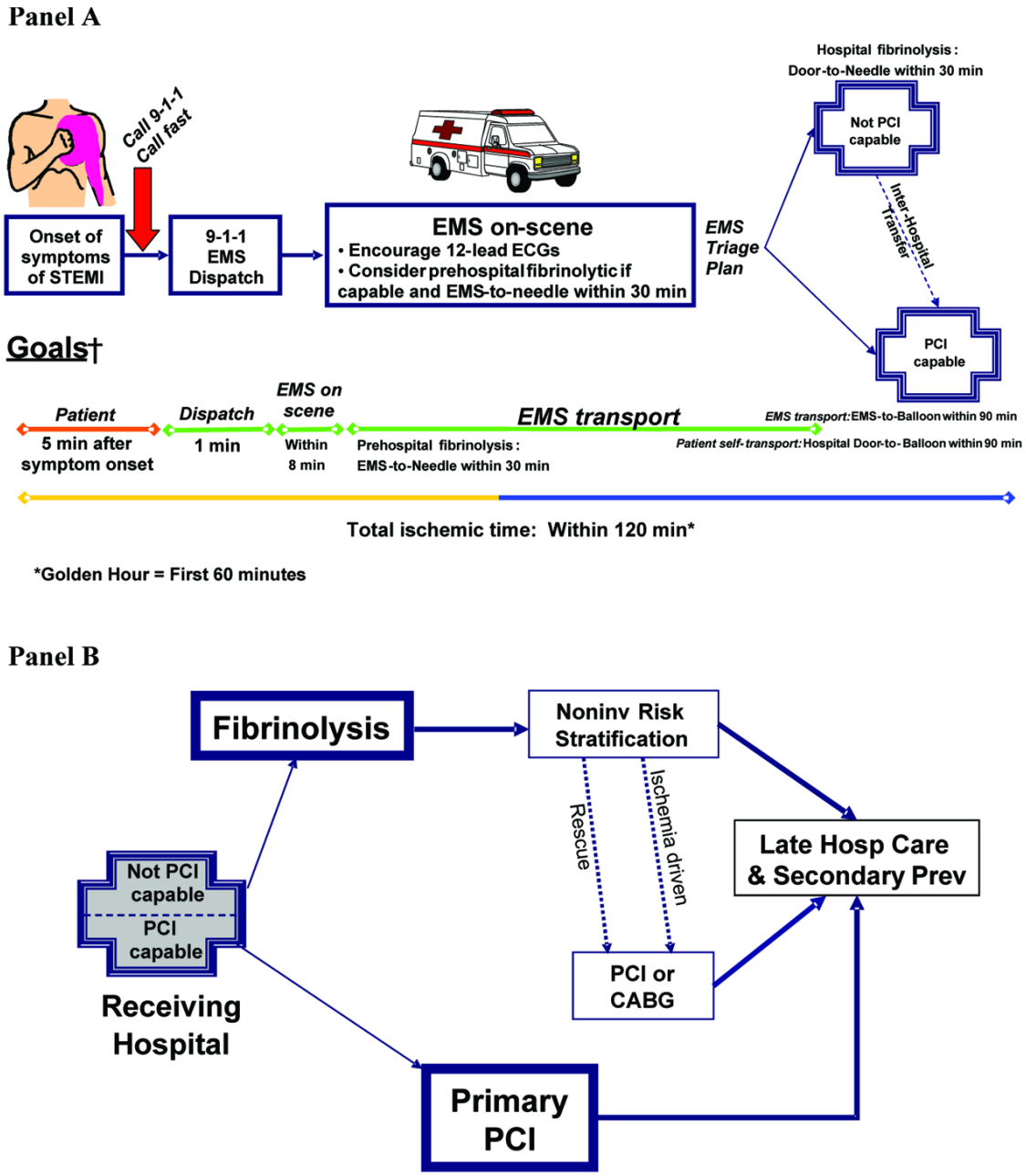


Figure 6. Options for transportation of patients with STEMI and initial reperfusion treatment. **Panel A:** Patient transported by EMS after calling 9-1-1: Reperfusion in patients with STEMI can be accomplished by the pharmacologic (fibrinolysis) or catheter-based (primary PCI) approaches. Implementation of these strategies varies based on the mode of transportation of the patient and capabilities at the receiving hospital. Transport time to the hospital is variable from case to case, but the goal is to keep total ischemic time within 120 min. There are 3 possibilities: 1) If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 min of EMS arrival on scene; 2) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a non–PCI-capable hospital, the hospital door-needle time should within 30 minutes for patients in whom fibrinolysis is indicated; 3) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the hospital door-to-balloon time should be within 90 min. Interhospital transfer: It is also appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization if: 1) there is a contraindication to fibrinolysis; 2) PCI can be initiated promptly (within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared to when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital); 3) fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI"). Secondary non-emergency interhospital transfer can be considered for recurrent ischemia. Patient self transport: Patient self-transportation is discouraged. If the patient arrives at a non-PCI capable hospital, the door-to-needle time should within 30 min. If the patient arrives at PCI-capable hospital, the door-to-balloon time should be within 90 min. The treatment options and time recommended after first hospital arrival are the same. **Panel B:** For patients who receive fibrinolysis, noninvasive risk stratification is recommended to identify the need for rescue PCI (failed fibrinolysis) or ischemia driven PCI. See Sections 6.3.1.6.4.5 and 6.3.1.6.7 in the full-text guidelines. Regardless of the initial method of reperfusion treatment, all patients should receive late hospital care and secondary prevention of STEMI. †The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI such that door-to-needle (or medical contact–to-needle) for initiation of fibrinolytic therapy can be achieved within 30 minutes or that 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. Modified with permission from Armstrong et al. Circulation 2003;107:2533-7 (155).

Table 3. Reperfusion Checklist for Evaluation of the Patient with STEMI

Step One: **Has patient experienced chest discomfort for greater than 15 min and less than 12 hours?**

YES → ***Step Two:***

NO → STOP

Step Two: **Are there contraindications to fibrinolysis?**
If ANY of the following are CHECKED "YES", fibrinolysis *MAY* be contraindicated.

Systolic BP greater than 180 mm Hg	**YES**	NO
Diastolic BP greater than 110 mm Hg	**YES**	NO
Right vs. left arm systolic BP difference greater than 15 mm Hg	**YES**	NO
History of structural central nervous system disease	**YES**	NO
Significant closed head/facial trauma within the previous 3 months	**YES**	NO
Recent (within 6 wks) major trauma, surgery (including laser eye surgery), GI/GU bleed	**YES**	NO
Bleeding or clotting problem or on blood thinners	**YES**	NO
CPR greater than 10 min	**YES**	NO
Pregnant female	**YES**	NO
Serious systemic disease (e.g., advanced/terminal cancer, severe liver or kidney disease)	**YES**	NO

Step Three: **Does the patient have severe heart failure or cardiogenic shock such that PCI is preferable?**

Pulmonary edema (rales greater than halfway up)	**YES**	NO
Systemic hypoperfusion (cool, clammy)	**YES**	NO

STEMI = ST-elevation myocardial infarction; BP = blood pressure; GI = gastrointestinal; GU = genitorurinary; CPR = cardiopulmonary resuscitation

Table 4. Prehospital and Inhospital Fibrinolysis

First Author and Reference	Year	Location	N	Design	Agent	End Points	Prehospital	Inhospital	p
McNeil (165)	1989	United Kingdom	57	R, PC, DB	Alteplase	Time to treatment (mean)	119 min	187 min	0.0005
						Confirmed MI	NR	NR	NR
						Cardiac mortality	7.4%	10%	NR
						EF (MUGA)	41%	35%	NR
Castaigne (166)	1989	France	93	R, PC	Anistreplase	Time to treatment (mean)	131 min	180 min	NR
						Confirmed MI	88%	NR	NR
						Inhospital mortality	3.5%	2.8%	NR
Barbash (167)	1990		87	R	Alteplase	Time to treatment (mean)	96 min	132 min	less than 0.0001
						Confirmed MI	NR	NR	NR
						Mortality (60 d) less than 120 min	0%	0%	NS
						Mortality (60 d) 120 min or greater	2.3%	6.8%	less than 0.01
						Discharge EF (MUGA)	50%	45%	NS
						CHF at discharge	4.6%	3.2%	0.07
Schofer (168)	1990		78	R, DB, PC	Urokinase	Time to treatment (mean)	85 min	137 min	less than 0.0005
						Confirmed MI	99%	NR	NR
						Inhospital mortality	2.5%	5.2%	NS
						Coronary patency prior to discharge	61%	67%	NS
						EF (LV angiography)	51%	53%	NS
						Bleeding (minor)	2.5%	5.2%	NS
McAleer (169)	1992		145	R	Streptokinase	Time to treatment (mean)	138 min	172 min	less than 0.02
						Confirmed MI	NR	NR	NR
						Mortality (14 d)	2.3%	11.5%	less than 0.05
						EF (MUGA)	57%	52%	NS
						Bleeding (minor)	18%	20%	NR

Continued on next page

Table 4. *Continued*

First Author and Reference	Year	Location	N	Design	Agent	End Points	Prehospital	Inhospital	p
Grampian Region Early Anistreplace Trial (GREAT) Group (170)	1992-94	Grampian Region of Scotland	311	R, DB, PC	Anistreplase	Time to treatment (mean)	101 min	240 min	NR
						Confirmed MI	99%	NR	NR
						Mortality (3 mo)	8%	15.5%	0.04
						Stroke	0.6%	0.6%	0.7
						Q-wave MI	53.3%	67.9%	0.02
						Q-wave MI (Rx less than 2 h)	50.0%	70.1%	0.01
						Q-wave MI (Rx greater than 2 h)	59.1%	64.4%	0.6
Weaver (159)	1993-96	Seattle	360	R, DB, PC	Alteplase	Time to treatment (mean)	77 min	110 min	less than 0.001
						Confirmed MI	98%	NR	NR
						Mortality (inhospital)	5.7%	8.1%	0.49
						EF (MUGA)	53%	54%	0.34
						SPECT infarct size	6.1%	6.5%	0.72
						Serious bleeding	6%	6%	NS
						Stroke	2.28%	1.08%	NS
European Myocardial Infarction Project (EMIP) Group (171)	1993-97	Europe, Canada	5469	R, DB	Anistreplase	Time to treatment (mean)	130 min	190 min	NR
						Confirmed MI	87%	NR	NR
						Mortality (30 d)	9.7%	11.1%	0.08
						Serious bleeding	1.2%	1.4%	NS
						Stroke	1.6%	1.5%	NS
Morrow (172)	1999-2001	United States	315	HC	Reteplase	Time to treatment (median)	EMS-1st rPA bolus = 31 min	EMS-inhospital lytic = 63 min	less than 0.0001
Bonnefoy* (173)	2000	France	840	R	Alteplase	Strategy	Prehospital lysis	Primary PCI	
						Time to treatment (median)	130 min	190 min	NS
						Death, MI, or stroke	8.2%	6.2%	0.29
						Death	3.8%	4.8%	0.61
						Reinfarction	3.7%	1.7%	0.13
						Disabling stroke	1%	0%	0.12

*Prehospital lysis versus primary PCI.

R = randomized; PC = placebo controlled; DB = double-blinded; MI = myocardial infarction; NR = not reported; NS = not significant; d = day; min = minute(s); EF = ejection fraction; MUGA = multigated radionuclide angiogram; CHF = congestive heart failure; LV = left ventricular; Rx = fibrinolytic therapy; SPECT = single-photon emission computed tomography; HC = historical control; EMS = emergency medical services; rPA = reteplase; PCI = percutaneous coronary intervention.

Modified with permission from Spinler and Mikhail. Ann Pharmacother 1997;31:1339-46 (174).

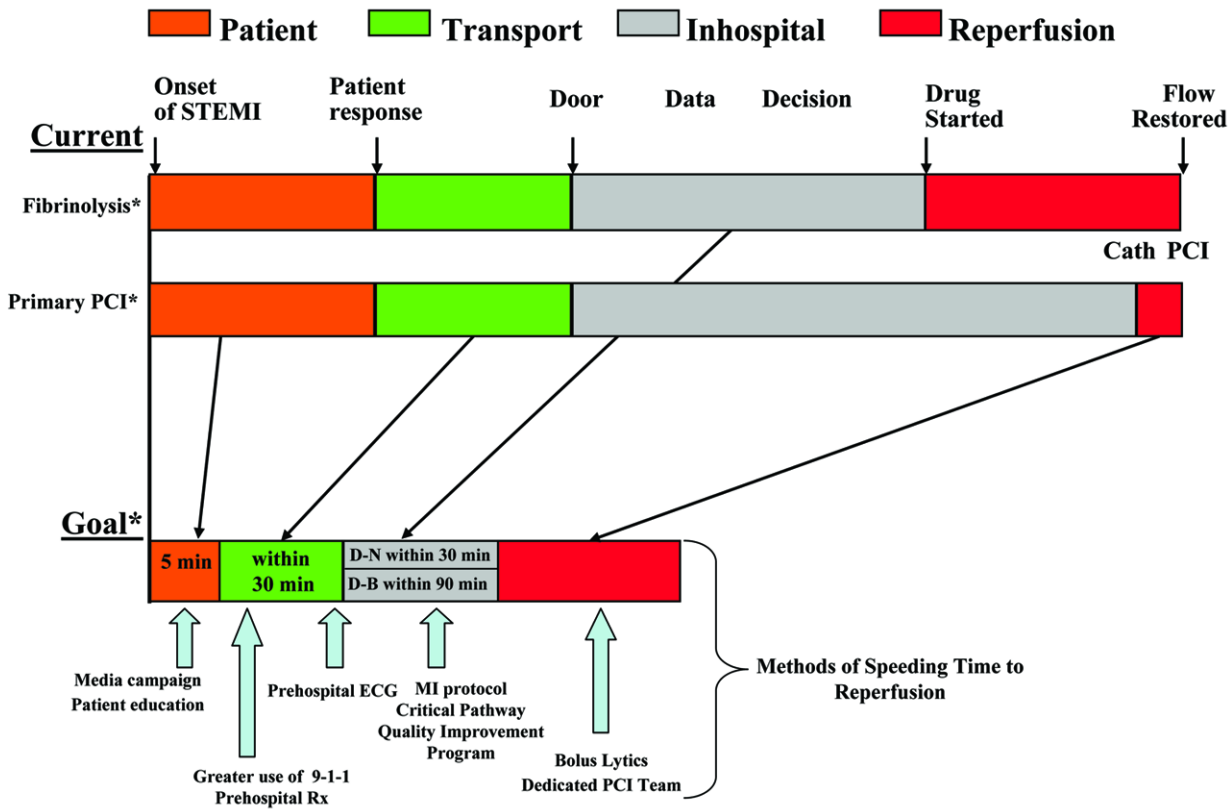


Figure 7. Major components of time delay between onset of symptoms from ST-elevation MI and restoration of flow in the infarct artery. Plotted sequentially from left to right are shown the time for patients to recognize symptoms and seek medical attention, transportation to the hospital, in-hospital decision-making, and implementation of reperfusion strategy, in time for restoration of flow once the reperfusion strategy has been initiated. The time to initiate fibrinolytic therapy is the "door-to-needle" (D-N) time; this is followed by the period of time required for pharmacologic restoration of flow. More time is required to move the patient to the catheterization laboratory for a percutaneous coronary interventional (PCI) procedure, referred to as the "door-to-balloon" (D-B) time, but restoration of flow in the epicardial infarct artery occurs promptly after PCI. At the bottom are shown a variety of methods for speeding the time to reperfusion along with the goals for the time intervals for the various components of the time delay. Cath = catheterization; PCI = percutaneous coronary intervention; min = minutes; ECG = electrocardiogram; MI = myocardial infarction; Rx = therapy. *These bar graphs are meant to be semiquantitative and not to scale. Modified with permission from Cannon et al. J Thromb Thrombol 1994;1:27-34 (180).

The difference between time to fibrinolytic therapy in the prehospital setting versus the hospital setting can be minimized by improved hospital triage with a decrease in door-to-needle time to within 30 minutes (179) (Figure 7) (180). However, only a small percentage (5% to 10%) of patients with chest pain in the prehospital setting have STEMI and are eligible for fibrinolytic therapy (159,181,182). Ensuring proper selection of patients for therapy can be difficult, and administration of therapy when it is contraindicated has important medical, legal, and economic implications. For these reasons, a general national policy of prehospital fibrinolytic therapy cannot currently be advocated. Prehospital fibrinolysis is reasonable in those settings in which physicians are present in the ambulance or prehospital transport times are more than 60 minutes in high-volume (more than 25 000 runs per year) EMS systems (102).

Other considerations for implementing a prehospital fibrinolytic service include the ability to transmit ECGs, paramedic initial and ongoing training in ECG interpretation and MI treatment, online medical command, and the presence of a medical director with training/experience in management of STEMI and full-time paramedics (183). An example of the time saved by prehospital fibrinolysis is illustrated in a report from Scotland. The National Health Service in the United Kingdom established the standard that patients thought to be suffering from STEMI should receive fibrinolysis within 60 minutes of calling for medical assistance (http://www.doh.gov.uk/nsf/coronarych3.htm). Three groups of patients in Scotland were studied: group 1 consisted of patients (n equals 107) within an urban area who received fibrinolytic therapy in the hospital, group 2 consisted of patients (n equals 43) from rural areas who received fibrinolytic therapy in the hospital, and group 3 consisted of patients (n equals 28) in a rural area who received fibrinolytic therapy (tenecteplase) in the ambulance by trained paramedics who were supervised by a medical control officer (183). Administration of prehospital fibrinolytic therapy resulted in a median time savings of 73 minutes compared with patients from rural areas and 28 minutes compared with patients from urban areas (p less than 0.001). A greater proportion of patients who received prehospital fibrinolytic ther-

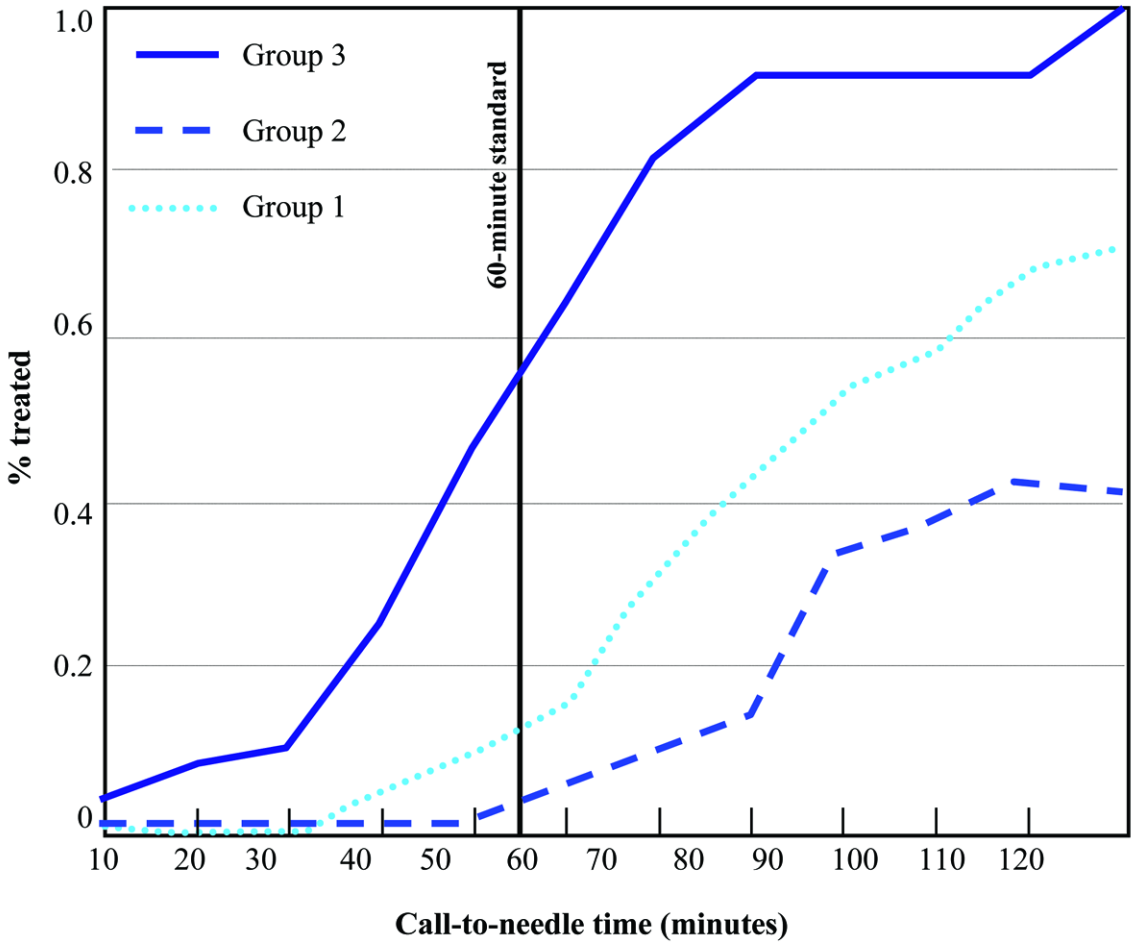


Figure 8. Cumulative distribution of call-to-needle time. Group 1 refers to patients from an urban area receiving fibrinolysis in the hospital. Group 2 are patients from rural areas who received fibrinolysis in the hospital. Group 3 are patients from the study area who received prehospital fibrinolysis. Modified from Pedley et al. BMJ 2003;327:22-6 (183) with permission from the BMJ Publishing Group.

apy were in compliance with the National Health Service standard of "call-to-needle" of 60 minutes (Figure 8) (183).

5.4. Prehospital Destination Protocols

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 (PCI or 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)***

Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed STEMI. Active involvement of local healthcare providers, particularly cardiologists and emergency physicians, is needed to formulate local EMS destination protocols for these patients. In general, patients

with suspected STEMI should be taken to the nearest appropriate hospital. However, patients with STEMI and shock are an exception to this general rule (Table 3).

Emergency revascularization improves 1-year survival in patients with STEMI complicated by cardiogenic shock (184). Subgroup analysis suggested a differential treatment effect, with the clearest benefit for those under 75 years of age. Therefore, whenever possible, patients with STEMI less than 75 years of age with shock should be transferred to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). On the basis of observations in the SHOCK Trial Registry and other registries, it is reasonable to extend such considerations of transfer to invasive centers for elderly patients with shock (see Section 7.6.5). Patients with STEMI who have contraindications to fibrinolytic therapy and an especially high risk of dying, including severe CHF or cardiogenic shock, 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). Given the importance of avoiding delays in time to reperfusion (see Section 6.3.1.6.3.1), direct transport to a facility capable of rapid revascularization is strongly preferred to interhospital transfer.

6. INITIAL RECOGNITION AND MANAGEMENT IN THE EMERGENCY DEPARTMENT

A variety of treatment options (Figure 3) (24-40) are available that can reduce mortality and morbidity in patients with STEMI, but the effectiveness of these therapies diminishes rapidly within the first several hours after symptoms onset (162,185). The traditional ED evaluation of patients with chest pain relies heavily on the patient's history, physical examination, and the ECG. This approach not infrequently fails to identify patients who are actually suffering from STEMI, which results in an inappropriate discharge home from the ED (186). Such missed MI patients are at relatively high risk of death or complications for the next 4 to 6 weeks after ED discharge (187-192).

In a large study on this subject, Pope et al. (188) found that 889 of 10 689 patients who presented to 10 US hospital EDs with chest pain or other symptoms that suggested acute cardiac ischemia had STEMI; 19 patients (2.1%, 95% CI 1.1% to 3.1%) were discharged from the ED. Patients with STEMI were more likely not to be hospitalized if they were nonwhite (odds ratio [OR] for discharge 4.5; 95% CI 1.8 to 11.8) or had a normal or nondiagnostic ECG (OR 7.7; 95% CI 2.9 to 20.2). The risk-adjusted mortality ratio for MI patients who were not hospitalized compared with those who were hospitalized was 1.9 (95% CI 0.7 to 5.2).

6.1. 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 ED with symptoms suggestive of STEMI. *(Level of Evidence: B)*

The advent of highly effective, time-dependent treatment for STEMI coupled with the need to reduce healthcare costs adds further incentive for clinicians to get the right answer quickly and to reduce unnecessary admissions and length of hospital stay. Investigators have tried various diagnostic tools such as clinical decision algorithms, cardiac biomarkers, echocardiography, and myocardial perfusion imaging in an attempt to avoid missing patients with MI or unstable angina. The most successful strategies to emerge thus far are designed to identify MI patients and, when clinically appropriate, screen for unstable angina and underlying coronary artery disease. Most strategies use a combination of cardiac biomarkers, short-term observation, diagnostic imaging, and provocative stress testing. An increasing number of high-quality centers now use structured protocols, checklists, or critical pathways to screen patients with suspected MI or unstable angina (193-205). It does not appear to matter whether the institution designates itself a chest pain center. Rather, it is the multifaceted, structured approach to the problem that appears to provide clinical, cost-effective benefit (206,207). One randomized trial has confirmed the safety, efficacy, and cost-effectiveness of the structured decision-making approach compared with standard, unstructured care (208).

6.2. Initial Patient Evaluation

Class I

1. **The delay from patient contact with the healthcare system (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 are unclear to the emergency**

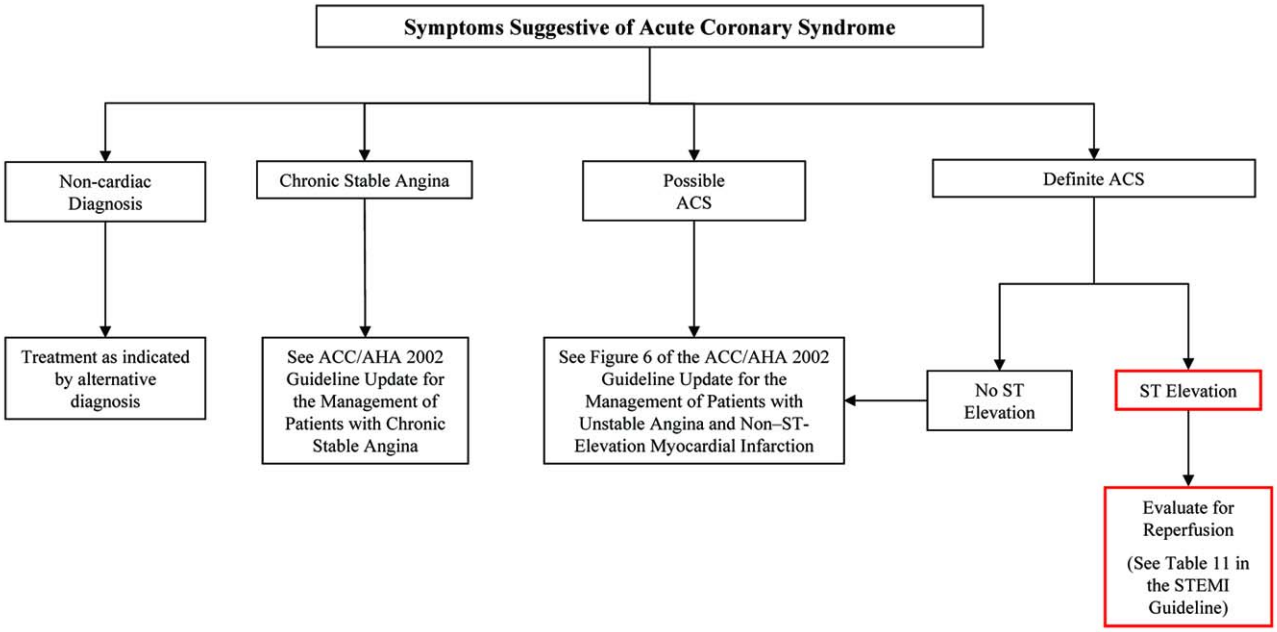


Figure 9. Algorithm for evaluation and management of patients suspected of having acute coronary syndrome. STEMI = ST-elevation myocardial infarction. Modified from Braunwald et al. J Am Coll Cardiol 2000;36:970-1062 (4).

physician or are not covered directly by the agreed-upon protocol, immediate cardiology consultation is advisable. ***(Level of Evidence: C)***

Regardless of the approach used, all patients presenting to the ED with chest discomfort or other symptoms suggestive of STEMI or unstable angina should be considered high-priority triage cases and should be evaluated and treated on the basis of a predetermined, institution-specific chest pain protocol. The protocol should include several diagnostic possibilities (Figure 9) (4). The patient should be placed on a cardiac monitor immediately, with emergency resuscitation equipment, including a defibrillator, nearby. An ECG should be performed and shown to an experienced emergency medicine physician within 10 minutes of ED arrival. If STEMI is present, the decision as to whether the patient will be treated with fibrinolytic therapy or primary PCI should be made within the next 10 minutes (Figure 7) (180). The goal for patients with STEMI should be to achieve a door-to-needle time of within 30 minutes and a door-to-balloon time of within 90 minutes (Figure 6) (155). If the initial ECG is not diagnostic, the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous ST-segment monitoring should be performed.

Ideally, such decisions should be made by the emergency medicine physician on duty in the ED based on a predetermined, institution-specific, written protocol that has been developed with input from cardiologists (both those involved in coronary care unit management and interventionalists), emergency medicine physicians, primary care physicians, nurses, and other appropriate personnel. For noninterventional hospitals, this will usually require formal, written transfer agreements and protocols that will permit expeditious transfer of patients who require urgent mechanical revascularization to the nearest appropriate interventional facility (Figure 6) (155). The protocol should also include the level of training and certification of personnel required to accompany the patient during transfer, the minimum equipment requirements, and the type(s) of transport vehicles (e.g., standard ground ambulance, mobile intensive care unit, helicopter, or fixed-wing aircraft) that can be used on the basis of patient condition. For cases in which the initial diagnosis and treatment plan are unclear to the emergency medicine physician or are not covered directly by the agreed-upon protocol, immediate cardiology consultation is advisable.

6.2.1. 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 angina, MI, coronary bypass surgery, 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)***

The history taken in the ED must be concise and detailed enough to establish the probability of STEMI but should be obtained expeditiously so as not to delay implementation of reperfusion therapy.

Chest Discomfort. The severity of discomfort varies and is typically graded on a scale of 1 to 10, with 10 being the most

severe pain. It is important to keep in mind that many patients will not admit having chest "pain" but will acknowledge the presence of chest "discomfort," because of their definition of pain. The chest discomfort is often described as a crushing, vice-like constriction, a feeling equivalent to an "elephant sitting on the chest," or heartburn. Usually, the discomfort is substernal but may originate in or radiate to areas such as the neck, jaw, interscapular area, upper extremities, and epigastrium. The duration of the discomfort, which typically lasts longer than 30 minutes, may wax and wane and may be remitting. It may be described as "indigestion in the chest" and occasionally may be relieved with belching. The possibility of precipitation of STEMI by use of illicit drugs such as cocaine should be considered.

The targeted history of patients with STEMI taken in the ED should ascertain whether the patient has had prior episodes of myocardial ischemia such as stable or unstable angina, MI, coronary bypass surgery, 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).

Associated Symptoms. Other symptoms to be aware of when taking a patient's history include nausea and vomiting. Diaphoresis associated with a pale complexion may also appear, as well as weakness or profound fatigue. Dizziness, lightheadedness, syncope, and paresthesia may occur because of pain and hyperventilation.

Hypertension. Hypertension should be assessed, because chronic, severe, poorly controlled hypertension or severe uncontrolled hypertension on presentation is a relative contraindication to fibrinolytic therapy (see Section 6.3.1.6.3.2).

Sex- and Age-Related Differences in Presentation. It has been noted in studies that women present with STEMI at an older age and later after the onset of symptoms than men (53,210). There must be an elevated index of suspicion during the evaluation of women for STEMI. Although some variation exists, when large databases of MI patients are examined, symptom profiles for STEMI by sex generally appear more similar than different between men and women (211-215). Elderly patients with STEMI are significantly less likely than younger patients to complain of chest discomfort. However, elderly patients with STEMI are more likely to complain of shortness of breath, as well as other atypical symptoms such as syncope or unexplained nausea. (181).

Diabetes Mellitus. Diabetics may have impaired angina (pain) recognition, especially in the presence of autonomic neuropathy. A diabetic may misinterpret dyspnea, nausea, vomiting, fatigue, and diaphoresis as disturbance of diabetic control. Up to 50% of diabetic individuals with type 2 diabetes for longer than 10 years will have autonomic nervous system dysfunction manifested by impaired heart rate variability. Diabetics with STEMI should be evaluated for renal dysfunction (216).

Possibility of Aortic Dissection. Severe tearing pain radiating directly to the back associated with dyspnea or syncope and without ECG changes indicative of STEMI should raise the suspicion for aortic dissection, and appropriate studies should be undertaken. Clinicians should have a heightened index of suspicion for aortic dissection in elderly hypertensive patients. However, it must be kept in mind that the dissection may extend to the pericardial sac and produce cardiac tamponade or disrupt the origin of a coronary artery.

Risk of Bleeding. Patients should be questioned about previous bleeding problems, e.g., during surgery or dental procedures, history of ulcer disease, cerebral vascular accidents, unexplained anemia, or melena. The use of antiplatelet, antithrombin, and fibrinolytic agents as part of the treatment for STEMI will exacerbate any underlying bleeding risks.

Clinical Cerebrovascular Disease. The patient with STEMI frequently has medical conditions that are risk factors for both MI and stroke. Evidence for prior episodes suggestive of clinical cerebrovascular disease should be sought. For example, the patient should be asked whether he/she has ever had symptoms of transient retinal or cerebral ischemia such as amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia, or vertigo. Transient ischemic attacks (TIAs) typically last less than 30 minutes, whereas symptoms that last more than 60 to 90 minutes are more likely to indicate the presence of a stroke (217). In addition, the patient should be asked whether he/she has ever had an ischemic stroke, intracerebral hemorrhage [ICH], or subarachnoid hemorrhage. A brief summary of the details for diagnosis of the different stroke subtypes is available (218). Finally, a history of cognitive decline/dementia may indicate the presence of cerebral amyloid angiopathy and increased risk of ICH, and information regarding head and facial trauma should be obtained.

6.2.2. Physical Examination

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)***

A brief physical examination may promote rapid triage (Table 5), whereas a more detailed physical examination aids in the differential diagnosis and is useful for assessing the extent, location, and presence of complications of STEMI (Tables 6 and 7) (219).

Table 5. Brief Physical Examination in the Emergency 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)

Evidence of prior stroke or dementia may be suggested by the finding on examination of focal neurological or cognitive deficits (Table 6). A brief but focused examination can identify focal neurological or cognitive deficits.

6.2.2.1. Differential Diagnosis

The differential diagnosis of STEMI includes conditions that can be exacerbated by fibrinolysis and anticoagulation (Table 8). The pain of aortic dissection is typically described as searing, ripping, or tearing and frequently radiates to the back or lower extremities. The pain is worse at onset and lasts for hours. Major pulses may be absent, and a murmur of aortic regurgitation may be present. A transesophageal echocardiogram, computed tomography (CT) scan, or magnetic resonance imaging scan is useful for establishing the diagnosis of aortic dissection. Active peptic ulcer disease can be present with chest or epigastric pain, sometimes radiating posteriorly, and may be associated with syncope, hematemesis, or melena. Free subdiaphragmatic air may be seen on upright chest X-ray in perforations. Acute pericarditis may show PR-segment depression and ST-segment elevation on the ECG but without reciprocal ST-segment depression (220). Pain from pericarditis is usually pleuritic and can radiate to the shoulder and trapezius ridge and is often relieved by sitting up and leaning forward, characteristics not found in STEMI. A rub is often present. Pulmonary embolus, with or without infarction, presents with dyspnea and knifelike pleuritic pain, sometimes with hemoptysis. Pulmonary embolism can present with chest pain similar to that of STEMI. Costochondral pain is described as sharp or sticking, with associated localized tenderness. Pneumothorax may present with acute dyspnea, pleuritic pain, and differential decrease in breath sounds with hyperresonance over 1 lung field. Acute cholecystitis may mimic STEMI, and right-upper-quadrant abdominal tenderness should be sought on physical examination.

6.2.3. Electrocardiogram

Class I

1. **A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 minutes of ED arrival on 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 RV infarction. (See Section 7.6.6 and the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography) *(Level of Evidence: B)***

Table 6. Physical Findings and Possible Implications in Complicated and Uncomplicated ST-Elevation Myocardial Infarction Patients

Cardiovascular
- General: Restless agitated, anguished facies, clenched fist (Levine's sign)
- Skin: Cool, clammy, pale, ashen
- Low-grade fever: Nonspecific response to myocardial necrosis
- Hypertension, tachycardia: High sympathetic tone (anterior MI)
- Hypotension, bradycardia: High vagal tone (inferior-posterior MI)
- Small-volume pulses: Low cardiac output
- Fast, slow, or irregular pulse: Atrial or ventricular arrhythmias, heart block
- Paradoxical "ectopic" systolic impulse: LV dyskinesis, ventricular aneurysm (anterior MI)
- Soft S_1: Decreased LV contractility; first-degree AV block (inferior MI)
- S_4 gallop: Decreased LV compliance
- Paradoxically split S_2: Severe LV dysfunction, LBBB
- S_3 gallop, pulmonary rales, pulsus alternans: LV systolic dysfunction (signs of CHF – greater than 25% of myocardium)
- Hypotension: Skin – cool, clammy, cyanotic; CNS – altered mental status; kidneys – oliguria (signs of cardiogenic shock)
- Jugular venous distension: with Kussmaul's sign, hypotension, RV S_4 and S_3 gallops, clear lungs (RV infarction)
- Systolic murmur of VSR: VSR (LSB, palpable thrill common)
- Differentiate from systolic murmur of MR: papillary muscle rupture
- Pericardial friction rub: Pericarditis (accompanies transmural MI) – late post-MI (Dressler's) syndrome
- Signs of cardiac tamponade, EM dissociation: Cardiac rupture
- Absent pulses and murmur of aortic regurgitation: Aortic dissection

Screening Neurological Examination
- Cognitive disorientation: memory loss, dysarthria, aphasia, hemispatial neglect
- Motor: facial asymmetry, pronator drift, reflex symmetry, limb dysmetria
- Sensory: loss of sensation of pinprick

MI = myocardial infarction; LV = left ventricular; AV = atrioventricular; LBBB = left bundle-branch block; CHF = congestive heart failure; CNS = central nervous system; RV = right ventricular; VSR = ventricular septal rupture; LSB = left sternal border; mitral regurgitation; EM = electromechanical.

The 12-lead ECG in the ED is at the center of the therapeutic decision pathway because of the strong evidence that

Table 7. Percent Mortality by Killip Class*

Killip Class	Killip and Kimball (Inhospital)	Fibrinolytic Trials (30 Days)			
		GISSI-1 (157)		International Study Group: Fibrinolytic (354)	ASSENT-2: Fibrinolytic (28)
		Placebo	Fibrinolytic		
I	6	7	6	5	5
II	17	20	16	18	13
III	38	39	33	32	26
IV	81	70	70	72	56†

Class I = no rales, no S_3; Class II = rales less than 50%; Class III = pulmonary edema; Class IV = cardiogenic shock.
*Values cited are subject to survivor bias.
†Highly selected group of patients.
Modified with permission from Topol. Textbook of Cardiovascular Medicine. 2nd ed. Philadelphia, PA: Lippincott-Williams & Wilkins; 2002:438 (219).

ST-segment elevation identifies patients who benefit from reperfusion therapy (221). Mortality increases with the number of ECG leads showing ST elevation. Important predictors of mortality on the initial 12-lead ECG include left bundle-branch block (LBBB) and anterior location of infarction (Figure 10) (222,223). Diagnostic criteria of greater than 0.1 mV in leads V_1 through V_4 may have reduced specificity for STEMI in patients with early repolarization. Some evidence exists to support the use of greater than or equal to 0.2 mV anteroseptal elevation as a preferable threshold for diagnosing STEMI, because a higher proportion of patients are correctly classified as having STEMI than with a threshold of greater than 0.1 mV in these leads (221).

Table 8. Differential Diagnosis of ST-Elevation Myocardial Infarction

Life-threatening
Aortic dissection
Pulmonary embolus
Perforating ulcer
Tension pneumothorax
Boerhaave syndrome (esophageal rupture with mediastinitis)
Other cardiovascular and nonischemic
Pericarditis
Atypical angina
Early repolarization
Wolff-Parkinson-White syndrome
Deeply inverted T waves suggestive of a central nervous system lesion or apical hypertrophic cardiomyopathy
LV hypertrophy with strain
Brugada syndrome
Myocarditis
Hyperkalemia
Bundle-branch blocks
Vasospastic angina
Hypertrophic cardiomyopathy
Other noncardiac
Gastroesophageal reflux (GERD) and spasm
Chest-wall pain
Pleurisy
Peptic ulcer disease
Panic attack
Biliary or pancreatic pain
Cervical disc or neuropathic pain
Somatization and psychogenic pain disorder

In the absence of ST elevation, there is no evidence of benefit of fibrinolytic therapy for patients with normal ECG or nonspecific changes, and there is some suggestion of harm (including increased bleeding risk) for patients with ST-segment depression only (221,224). Notwithstanding this, fibrinolytic therapy may be appropriate when there is marked ST-segment depression confined to leads V_1 through V_4 and accompanied by tall R waves in the right precordial leads and upright T waves indicative of a true posterior injury current and circumflex coronary occlusion. In circumstances where there is a suggestive clinical history and suggestive evidence of true posterior infarction, confirmatory data from posterior leads (i.e., V_7 and V_8) as well as 2-dimensional echocardiography may be especially helpful; this latter investigation has a high negative predictive value (225,226). Primary PCI is another reperfusion strategy that may be effective in patients with true posterior MI (see Section 6.3.1.6.4.2).

Initial errors in ECG interpretation can result in up to 12% of patients being categorized inappropriately, demonstrating a potential benefit of accurate computer-interpreted electrocardiography and fax transmission to an expert (227). It is less likely that STEMI is present if the upward-directed ST-segment changes are concave rather than convex (228).

Because lethal ventricular arrhythmias may develop abruptly in patients with STEMI, all patients should be monitored electrocardiographically on arrival in the ED. It is important to examine serial tracings approximately 5 to 10 minutes apart, or if symptoms recur, during evaluation in the ED for development of ST elevation if the initial ECG is nondiagnostic. ST elevation may also be detected by intermittent visual inspection of the oscilloscope or auditory alarms in systems with continuous ST-segment monitoring capability.

Although the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group overview indicates that patients with new or presumably new LBBB are at high risk when presenting with presumed MI, this ECG presentation is a frequent cause of delay or lack of reperfusion therapy because of the concern of the validity of the ECG criteria for MI diagnosis and the risk of therapy. This is also a situation in which direct PCI may be preferable to fibrinolytic therapy (156). It has been suggested that patients with new or presumably new LBBB coupled with a typical ischemic history be approached with a plan to rule in MI using 1 of 3 ECG crite-

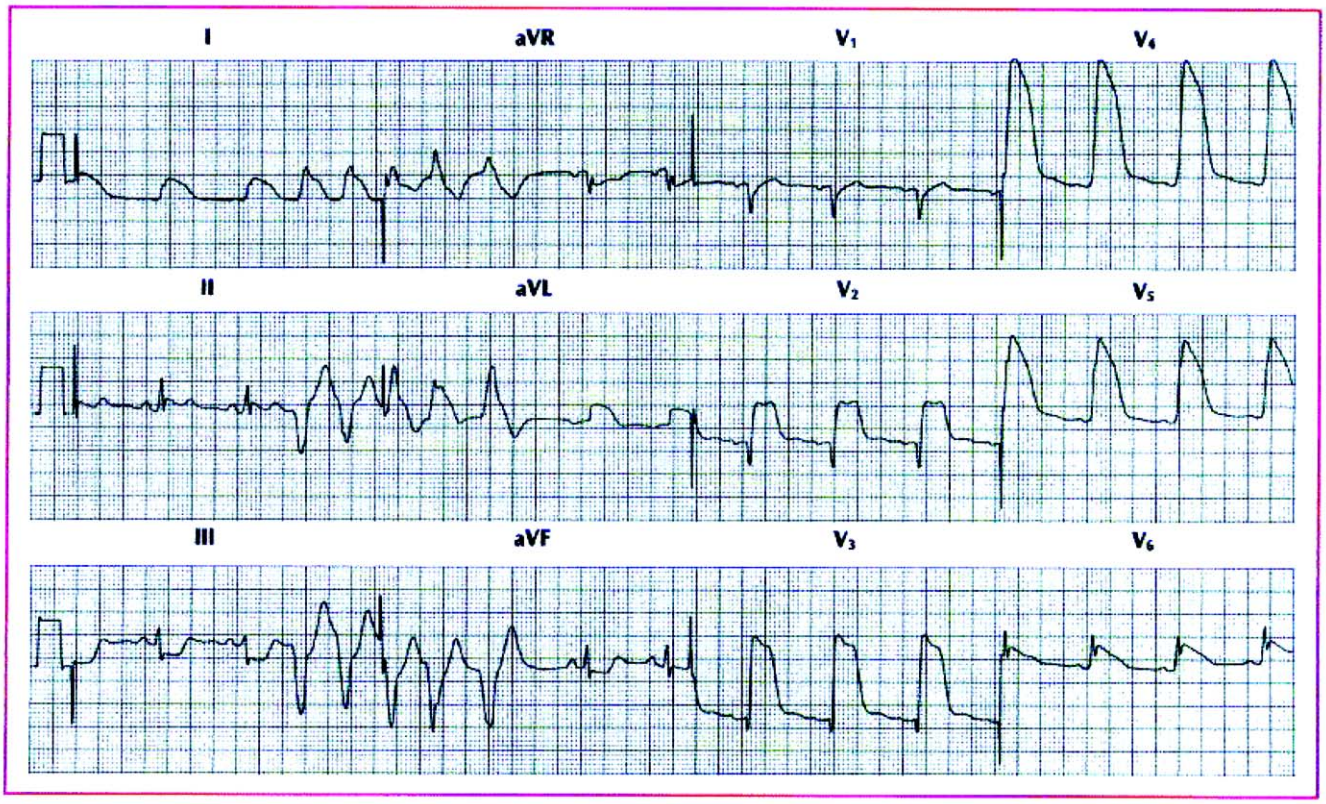


Figure 10. Risk stratification: electrocardiogram (ECG). This 12-lead ECG was obtained from a middle-aged man admitted with an extensive anterior acute myocardial infarction. (Note pathological Q waves in the precordial leads and marked repolarization abnormalities in the anterior and lateral leads.) A 5-beat salvo of non-sustained VT is seen extending over the transition between leads III and aVF. Reprinted with permission from Antman and Rutherford. Coronary Care Medicine. Boston, MA: Martinus Nijhoff Publishing; 1986:81 (223).

ria that provide independent diagnostic value. These consist of ST elevation greater than or equal to 0.1 mV in leads with a positive QRS, ST depression greater than or equal to 0.1 mV in V_1 to V_3, and ST elevation greater than or equal to 0.5 mV in leads with a negative QRS (229,230).

6.2.4. 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. For specific laboratory examinations, see Table 9. *(Level of Evidence: C)*

Table 9. Laboratory Evaluations for Management of ST-Elevation Myocardial Infarction

Serum biomarkers for cardiac damage (do not wait for results before implementing reperfusion strategy)
CBC with platelet count
INR
aPTT
Electrolytes and magnesium
BUN
Creatinine
Glucose
Serum lipids

CBC = complete blood count; INR = international normalized ratio; aPTT = activated partial thomboplastin time; BUN = blood urea nitrogen.

In addition to serum cardiac biomarkers for cardiac damage, several routine evaluations have important implications for management of patients with STEMI (Table 9). Although these studies should be undertaken when the patient is first examined, therapeutic decisions should not be delayed until results are obtained because of the crucial role of time to therapy in STEMI.

6.2.5. 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

Table 10. Molecular Biomarkers for the Evaluation of Patients With ST-Elevation Myocardial Infarction

Biomarker	Molecular Weight, Da	Range of Times to Initial Elevation, h	Mean Time to Peak Elevations (Nonreperfused)	Time to Return to Normal Range
Frequently used in clinical practice				
CK-MB	86 000	3-12 h	24 h	48-72 h
cTnI	23 500	3-12 h	24 h	5-10 d
cTnT	33 000	3-12 h	12 h–2 d	5-14 d
Infrequently used in clinical practice				
Myoglobin	17 800	1-4 h	6-7 h	24 h
CK-MB tissue isoform	86 000	2-6 h	18 h	Unknown
CK-MM tissue isoform	86 000	1-6 h	12 h	38 h

Da = Daltons; h = hours; CK-MB = MB isoenzyme of creatine kinase; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CK-MM = MM isoenzyme of creatine kinase.
Modified with permission from Adams et al. Circulation 1993;88:750 (232).

not undergoing angiography within the first 24 hours after fibrinolytic therapy. *(Level of Evidence: B)*

Class III

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

The nomenclature of acute coronary syndromes is illustrated in Figure 2 (8-10). The central position of the 12-lead ECG and initial triage of patients are emphasized. Serum cardiac biomarkers (creatine kinase [CK], CK-MB, cardiac-specific troponins, myoglobin) are useful for confirming the diagnosis of MI and estimating infarct size. Serum cardiac biomarkers also provide valuable prognostic information. For patients with ST-segment elevation, the diagnosis of STEMI is secure; initiation of reperfusion therapy should not be delayed while awaiting the results of a cardiac biomarker assay (231,232) (Table 10). Quantitative analysis of cardiac biomarker measurements provides prognostic information as well as a noninvasive assessment of the likelihood that the patient has undergone successful reperfusion when fibrinolytic therapy is administered (Figure 11) (233,234).

Because there are differences in the clinical need for biomarkers in STEMI versus NSTEMI patients and differences in the characteristics of the various cardiac biomarkers, preferential use of a particular biomarker should be based on the clinical syndrome. CK-MB is found in the skeletal muscle and blood of healthy subjects; therefore, the cutoff value for an elevated CK-MB is typically set a few units above the upper end of the reference (normal) range. In contrast, because cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are not normally detected in the blood of healthy people, the definition of an abnormally increased level is a value that exceeds that of 99% of a reference control group. Given the nearly absolute myocardial tissue specificity and high sensitivity for even microscopic zones of myocardial necrosis, the ACC and the European Society of Cardiology subsequently declared cardiac troponins to be the preferred biomarker for diagnosing MI (233). A single cutoff point was recommended such that an MI would be diagnosed if, as a result of myocardial ischemia, cTnI or cTnT were detected at least once within 24 hours of the index clinical event at a level exceeding the 99th percentile of the mean value measured in a normal control population (233). The superior sensitivity makes troponin the preferred marker for patients with UA/NSTEMI. In contrast, patients with STEMI are recognized on the basis of the 12-lead ECG, and in general, subsequent confirmation of MI can be ascertained by measurement of any of the available cardiac biomarkers. Occasionally, a very small infarct will be missed by CK-MB; therefore, troponin should be measured for patients suspected to have STEMI who have negative serial CK-MBs.

It should be recognized that in patients with STEMI, cTnT and cTnI may first begin to rise above the reference limit by 3 to 6 hours from the onset of ischemic symptoms. Therefore, a significant number of patients will present to the emergency room with negative biomarkers. Myoglobin, a low-molecular-weight heme protein found in cardiac and skeletal muscle, is not cardiac specific but is released more rapidly from infarcted myocardium than CK-MB and may be detected as early as 2 hours after STEMI.

In some patients, cardiac-specific troponins may not be detectable for up to 6 hours after onset of chest pain. Thus, when CK-MB, cTnI, or cTnT levels are elevated in less than 6 hours after the onset of discomfort in patients with STEMI, clinicians should suspect that an antecedent episode of unstable angina was in fact MI and the patient is exhibiting a stuttering course of occlusion and release of the infarct artery. Data from the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) III Study suggest that patients with STEMI who have elevated cTnT levels and who are less than 6 hours from the onset of discomfort have an increased mortality risk (235).

CK-MB is the preferred, widely available cardiac biomarker for most patients with STEMI, for whom the need to diagnose reinfarction and noninvasively assess reperfusion is

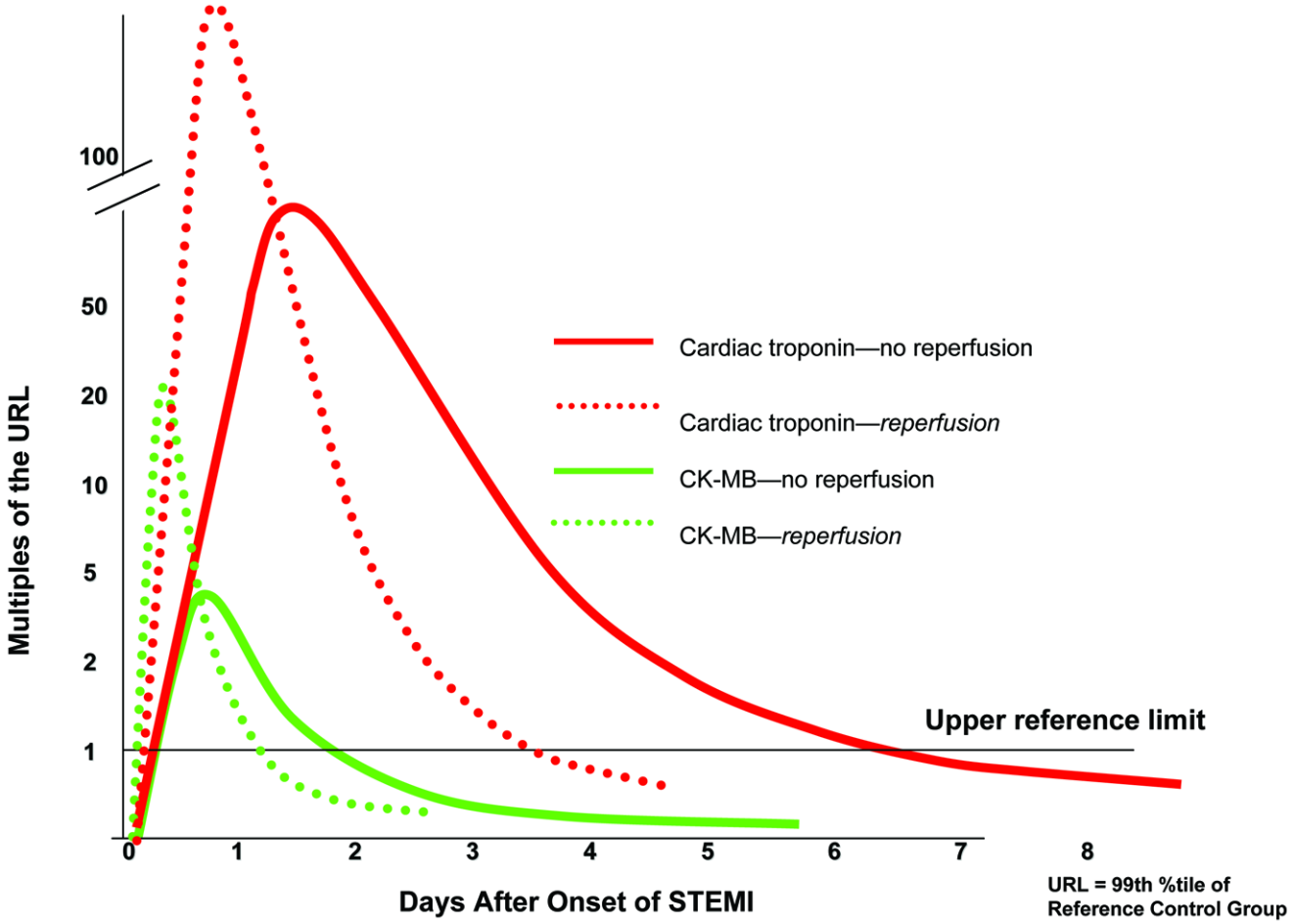


Figure 11. Cardiac biomarkers in ST-elevation myocardial infarction (STEMI). Typical cardiac biomarkers that are used to evaluate patients with STEMI include the MB isoenzyme of CK (CK-MB) and cardiac specific troponins. The horizontal line depicts the upper reference limit (URL) for the cardiac biomarker in the clinical chemistry laboratory. The URL is that value representing the 99th percentile of a reference control group without STEMI. The kinetics of release of CK-MB and cardiac troponin in patients who do not undergo reperfusion are shown in the solid green and red curves as multiples of the URL. Note that when patients with STEMI undergo reperfusion, as depicted in the dashed green and red curves, the cardiac biomarkers are detected sooner, rise to a higher peak value, but decline more rapidly, resulting in a smaller area under the curve and limitation of infarct size. Modified with permission from Alpert et al. J Am Coll Cardiol 2000;36:959 (233) and Wu et al. Clin Chem 1999;45:1104 (234).

greater than the need to make the diagnosis. By mapping the time course of the rise and fall of a biomarker (typically CK-MB), clinicians can detect an interruption of the progressive fall of the biomarker level to a point below the upper reference limit (Figure 11) (233,234). Re-elevation of the biomarker level is evidence of myocardial reinfarction (Figure 12). A more rapidly rising and falling biomarker such as CK-MB or myoglobin is superior for diagnosing reinfarction. As a consequence of continuous release from a degenerating contractile apparatus in necrotic myocytes, elevations of cTnI may persist for 7 to 10 days after MI, and elevations of cTnT may persist for up to 10 to 14 days. The more protracted time course of kinetic release of cTnI and cTnT limits the ability of clinicians to make the diagnosis of reinfarction within several days after the index STEMI event. An algorithm illustrating the decision-making process that incorporates biomarker measurements, ECG findings, clinical symptoms, and, if available, autopsy data for making the diagnosis of reinfarction is shown in Figure 12.

In addition to monitoring the patient for resolution of ischemic-type chest discomfort and regression of the magnitude of ST-segment elevation on the ECG, clinicians can obtain serial measurements of serum cardiac markers to buttress the noninvasive diagnosis of reperfusion of the infarct-related artery after fibrinolytic therapy (Figure 11) (233,234,236). An early peak of CK-MB (12 to 18 hours) suggests reperfusion. Because of its rapid-release kinetics, myoglobin is also an attractive marker for the early diagnosis of reperfusion.

CK-MB isoforms are another serum cardiac biomarker less frequently used for evaluating patients with STEMI. CK-MB exists in only 1 form in myocardial tissue but in different isoforms (or subforms) in the plasma. An absolute level of CK-MB2 greater than 1 U/L or a ratio of CK-MB2 to CK-MB1 of 1.5 has improved sensitivity and specificity for diagnosis of MI within the first 6 hours compared with conventional assays for CK-MB (237).

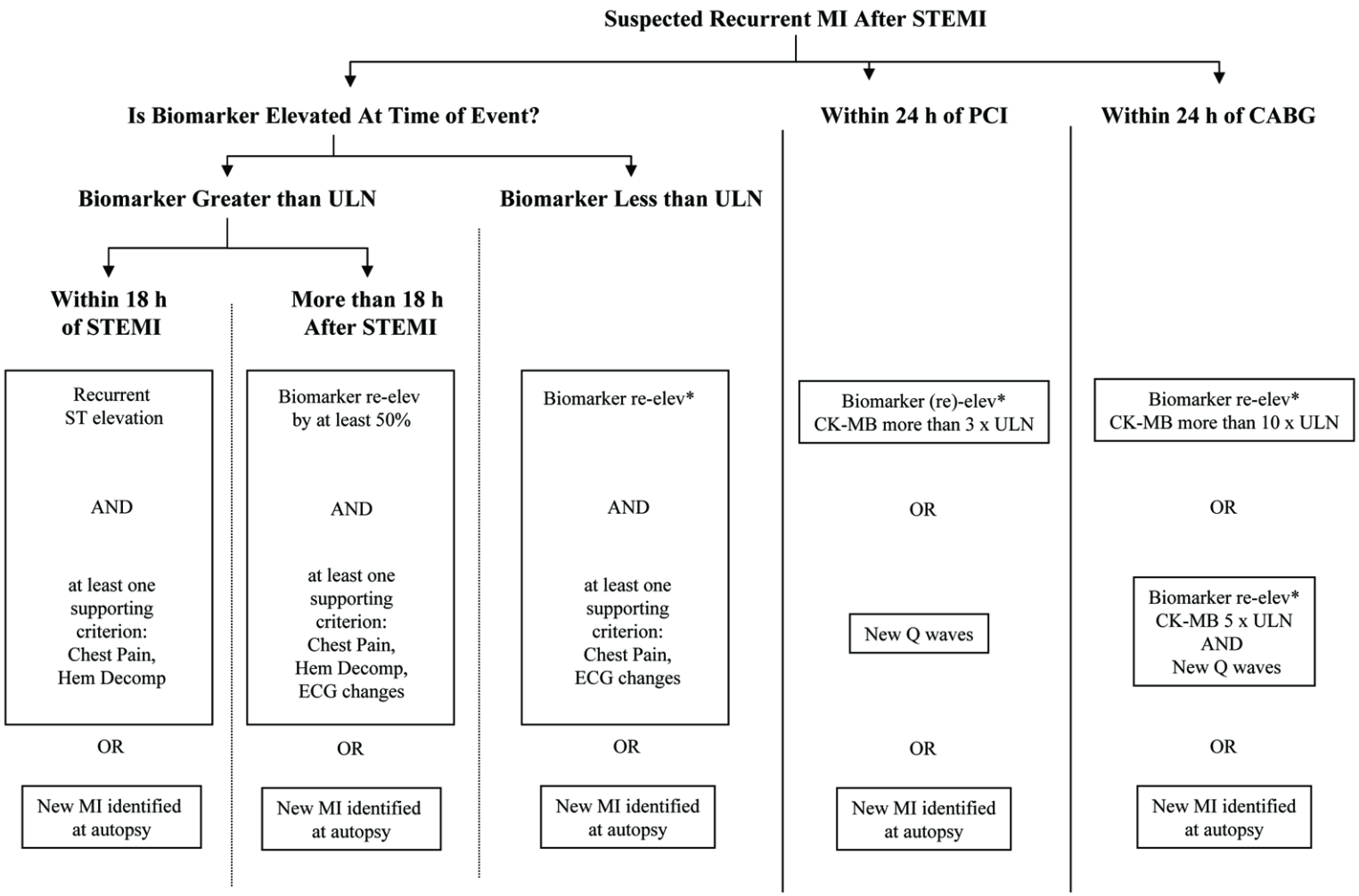


Figure 12. Algorithm for diagnosing recurrent MI after the index STEMI event. MI = myocardial infarction; STEMI = ST-elevation MI; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; h = hours; Hem Decomp = hemodynamic decompensation; CK-MB = MB isoenzyme of creatine kinase; ULN = upper limit of normal; re-elev = re-elevated; ECG = electrocardiogram. * Because of a more protracted time course of elevations after the index STEMI event, diagnosis of recurrent MI may be problematic if cardiac troponins are used. A more rapidly rising and falling cardiac biomarker such as CK-MB is preferable.

6.2.5.1. 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 done 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)***

Handheld rapid bedside assays are clinically available for measuring cTnI, cTnT, myoglobin, and CK-MB, but in general, bedside assays are less sensitive and less precise than quantitative assays. Small desktop rapid analyzers are also available for the same purpose. A rapid, high-voltage electrophoretic system is available for measuring CK-MB isoforms. Monitoring the timing of the appearance of a positive bedside assay result may provide clinicians with a tool for a semiquantitative estimate of a serum cardiac biomarker level at the patient's bedside (238). A positive bedside test should be confirmed by a conventional quantitative test. However, reperfusion therapy should not be delayed while one awaits the results of a quantitative assay.

6.2.6. 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 is suspected, such as aortic dissection). *(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 CT scan or magnetic resonance imaging scan should be used for differentiating 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 who present to the ED, especially if the diagnosis of STEMI is confounded by LBBB or pacing or if there is suspicion of posterior STEMI with anterior ST depressions. (See Section 7.6.7, Mechanical Causes of Heart Failure/Low-Output Syndrome.) *(Level of Evidence: B)*

Class III

Single-photon emission CT (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)*

Various forms of imaging are often used to evaluate patients with symptoms that are suggestive of MI or acute coronary syndrome. Cardiac imaging can be of value in further determining the cause of chest discomfort in patients suspected of having an acute MI or unstable angina but whose initial ECG is normal or nondiagnostic. The 2 most studied techniques thus far have been echocardiography and radionuclide imaging.

Bedside echocardiography is useful for diagnosis and risk stratification of chest pain patients in the ED (226). A high-quality portable chest X-ray, transthoracic and/or transesophageal echocardiography, and a contrast chest CT scan can be useful for differentiating acute MI from aortic dissection in patients for whom this distinction is clinically unclear.

SPECT radionuclide imaging at rest is not routinely indicated to establish the diagnosis of MI in patients with STEMI, although it can provide valuable, accurate diagnostic and prognostic information in patients who present to the ED with symptoms suggestive of acute cardiac ischemia and a normal or nondiagnostic ECG (239). During the recuperative phase of hospitalization for STEMI, SPECT imaging can be used to study myocardial perfusion and to look for segmental abnormalities of LV wall motion.

6.2.7. Global Risk Assessment Tools

Global risk assessment provides an opportunity to integrate various patient characteristics into a single score that can convey an overall estimate of a patient's prognosis over a given period of time. Beyond being informative about prognosis, the general value of these risk assessment tools is that they can influence clinical strategies. In general, the risk of the intervention should be commensurate with the underlying risk of the patient without the intervention and the expected benefit of the intervention. That is, a high-risk intervention should usually not be used for a very low-risk patient. The expected increase in risk associated with the intervention would very likely outweigh the expected benefit.

Several risk assessment tools have been proposed for patients with STEMI (240-243). One such tool uses clinical and ECG characteristics to predict risk of mortality for a patient if and if not treated with fibrinolytic therapy, as well as the risk of intracranial hemorrhage and major bleeding. This decision aid suggests that some patients with small infarctions may not have a substantial benefit from fibrinolytic therapy, particularly those who may have a risk factor for bleeding. These estimates are based on trials and registries. The use of this aid in clinical practice did not increase the use of fibrinolytic therapy overall (244). Whether the widespread application of these tools can improve decision making is not clear. Nevertheless, they provide estimates of risk that may be useful in the tailoring of therapy for individual patients. In general, however, patients who present with STEMI require evaluation for rapid reperfusion therapy

and treatment with aspirin, beta-blockers, and ACE inhibitors. Nevertheless, any patient with a risk from the intervention that exceeds their STEMI risk reduction will, on average, do better without that treatment. This group will generally include patients with a higher risk from the intervention or a lower absolute risk reduction (generally because of a low absolute STEMI risk). This issue may be particularly important for younger patients, who tend to have a lower absolute risk of mortality (245), and for the elderly, who tend to have a higher risk from interventions, particularly with respect to fibrinolytic therapy (246). Precise estimates of risks and benefits are useful because the low STEMI risk in younger patients is often accompanied by a lower risk of interventions. In contrast, in the elderly, the higher intervention risk is accompanied by a higher STEMI risk (and thus a larger absolute reduction in risk with the intervention) (247).

The use of any risk assessment tool should not contribute to any delay in providing the time-sensitive assessment and treatment strategies that patients with STEMI require. Further research is necessary to determine how these tools may best contribute to optimizing patient outcomes.

6.3. Management

6.3.1. Routine Measures

6.3.1.1. 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)*

It has become universal practice to administer oxygen, usually by nasal prongs, to virtually all patients suspected of having acute ischemic-type chest discomfort, although it is not known whether this therapy limits myocardial damage or reduces morbidity or mortality. If oxygen saturation monitoring is used, therapy with supplemental oxygen is indicated if the saturation is less than 90%. Experimental results indicate that breathing oxygen may limit ischemic myocardial injury (248), and there is evidence that oxygen administration reduces ST-segment elevation (249). The rationale for use of oxygen is based on the observation that even with uncomplicated MI, some patients are modestly hypoxemic initially, presumably because of ventilation-perfusion mismatch and excessive lung water (250).

In patients with severe congestive heart failure, pulmonary edema, or a mechanical complication of STEMI, significant hypoxemia may not be corrected with supplemental oxygen alone. Continuous positive-pressure breathing or endotracheal intubation and mechanical ventilation may be required in such cases (251).

For patients without complications, excess administration of oxygen can lead to systemic vasoconstriction, and high flow rates can be harmful to patients with chronic obstructive airway disease. In the absence of compelling evidence for established benefit in uncomplicated cases, and in view of its expense, there appears to be little justification for continuing its routine use beyond 6 hours.

6.3.1.2. Nitroglycerin

Class I

1. **Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of 3 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 beats per minute [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)***

The physiological effects of nitrates include reducing preload and afterload through peripheral arterial and venous dilation, relaxation of epicardial coronary arteries to improve coronary flow, and dilation of collateral vessels, potentially creating a more favorable subendocardial to epicardial flow ratio (252-254). Vasodilation of the coronary arteries, especially at or adjacent to sites of recent plaque disruption, may be particularly beneficial for the patient with acute infarction. Nitrate-induced vasodilatation may also have particular utility in those rare patients with coronary spasm presenting as STEMI.

Clinical trial results have suggested only a modest benefit from nitroglycerin used acutely in STEMI and continued subsequently. A pooled analysis of more than 80 000 patients treated with nitrate-like preparations intravenously or orally in 22 trials revealed a mortality rate of 7.7% in the control group, which was reduced to 7.4% in the nitrate group. These data are consistent with a possible small treatment effect of nitrates on mortality such that 3 to 4 fewer deaths would occur for every 1000 patients treated (152).

Nitroglycerin may be administered to relieve ischemic pain and is clearly indicated as a vasodilator in patients with STEMI associated with LV failure. Nitrates in all forms should be avoided in patients with initial systolic blood pressures less than 90 mm Hg or greater than or equal to 30 mm Hg below

baseline, marked bradycardia or tachycardia (256), or known or suspected RV infarction. Patients with RV infarction are especially dependent on adequate RV preload to maintain cardiac output and may experience profound hypotension during administration of nitrates (257). Phosphodiesterase inhibitors potentiate the hypotensive effects of nitrates because of their mechanism of action in releasing nitric oxide and increasing cyclic guanosine monophosphate (258). Therefore, it is useful clinical practice to ascertain whether such agents have been used, and nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction in the prior 24 hours (48 hours for tadalafil).

Nitroglycerin is commonly given sublingually at doses of 0.4 mg when patients present with STEMI. Arterial pressure may decline precipitously because of limited control of the initial dose and rate of absorption. An intravenous infusion of nitroglycerin allows clinicians to titrate the therapy in response to the patient's blood pressure. A useful intravenous nitroglycerin regimen employs an initial infusion rate of 5 to 10 mcg per minute with increases of 5 to 20 mcg per minute until symptoms are relieved or mean arterial blood pressure is reduced by 10% of its baseline level in normotensive patients and by up to 30% for hypertensive patients, but in no case below a systolic pressure of 90 mm Hg or a drop greater than 30 mm Hg below baseline. In view of their marginal treatment benefits, nitrates should not be used if hypotension limits the administration of beta-blockers, which have more powerful salutary effects.

6.3.1.3. Analgesia

Class I

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)*

Pain relief is an important element in the early management of the patient with STEMI. There is a tendency to underdose patients with STEMI because of the desire to assess the response to anti-ischemic or reperfusion therapy. This should be avoided, because patients with STEMI have a hyperadrenergic state particularly early after the onset of coronary occlusion. Conversely, it should not be assumed that resolution of discomfort after administration of analgesics indicates reperfusion has occurred (see Section 6.3.1.6.3.7 for further discussion). Pain, which is commonly severe in the acute phase of the event, contributes to increased sympathetic activity.

Pain management should be directed toward acute relief of symptoms of ongoing myocardial ischemia and necrosis and toward general relief of anxiety and apprehension, the latter of which can heighten pain perception. Surges of catecholamines have been implicated as having a role in plaque fissuring and thrombus propagation and in reducing the threshold for ventricular fibrillation (259). Because the pain of STEMI is related to ongoing ischemia, interventions that affect the oxygen supply-demand relationship (i.e., by either increasing supply or decreasing demand) may lessen the pain of STEMI (260).

Control of cardiac pain is typically accomplished with a combination of nitrates, opiate analgesic agents, oxygen, and beta-adrenergic blockers. Treatment with these agents extends from the ED to the critical care unit. An important consideration when using intravenous nitrates is not to lower blood pressure to a level that would preclude adequate dosage of morphine sulfate for pain control. Morphine sulfate remains the analgesic agent of choice for management of pain associated with STEMI, except in documented cases of morphine sensitivity. The dose required for adequate pain relief varies in relation to age and body size, as well as blood pressure and heart rate. Anxiety reduction secondary to morphine administration reduces the patient's restlessness and the activity of the autonomic nervous system, with a consequent reduction of the heart's metabolic demands. Morphine administration for patients with pulmonary edema is clearly beneficial and may promote peripheral arterial and venous dilation, reducing the work of breathing and slowing the heart rate secondary to combined withdrawal of sympathetic tone and augmentation of vagal tone (259,260).

Side effects of morphine administration such as hypotension can be minimized by keeping the patient supine and elevating the lower extremities if systolic pressure goes below 100 mm Hg systolic, assuming pulmonary edema is not present. The concomitant use of atropine in 0.5- to 1.5-mg doses intravenously may be helpful in reducing the excessive vagomimetic effects of morphine if significant bradycardia or hypotension occurs. Although respiratory depression is relatively uncommon, patients' respirations should be monitored, particularly as their cardiovascular status improves. The narcotic reversing agent naloxone, 0.1 to 0.2 mg intravenously, can be given initially if indicated and repeated after 15 minutes if necessary. Nausea and vomiting as potential side effects of large doses of morphine may be treated with a phenothiazine (260).

See "Hospital Management" (Section 7.2.4) for additional discussion of analgesia.

6.3.1.4. 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.

At a dose of 162 mg or more, aspirin produces a rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A_2 production. The Second International Study of Infarct Survival (ISIS-2) has shown conclusively the efficacy of aspirin alone for treatment of evolving acute MI, with an absolute risk difference in 35-day mortality of 2.4% (relative risk reduction [RRR] 23%) (261).

When aspirin was combined with streptokinase, the absolute risk difference in mortality was 5.2% (RRR 42%). A meta-analysis demonstrated that aspirin reduced coronary reocclusion and recurrent ischemic events after fibrinolytic therapy with either streptokinase or alteplase (262). Accordingly, aspirin now forms part of the early management of all patients with suspected STEMI and should be given promptly, certainly within the first 24 hours, at a dose between 162 and 325 mg and continued indefinitely at a daily dose of 75 to 162 mg (263). Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations (264).

Unlike fibrinolytic agents, there is little evidence for a time-dependent effect of aspirin on early mortality. However, data do support the contention that a chewable aspirin is absorbed more quickly than one swallowed in the early hours after infarction, particularly after opiate therapy. The use of aspirin is contraindicated in those with a hypersensitivity to salicylate. Aspirin suppositories (300 mg) can be used safely and are the recommended route of administration for patients with severe nausea and vomiting or known upper-gastrointestinal disorders. In patients with true aspirin allergy (hives, nasal polyps, bronchospasm, or anaphylaxis), clopidogrel or ticlopidine may be substituted.

6.3.1.5. Beta-Blockers

Class I

Oral beta-blocker therapy should be administered promptly to those patients without a contraindication, irrespective of concomitant fibrinolytic therapy or performance of primary PCI. *(Level of Evidence: A)*

Class IIa

It is reasonable to administer IV beta-blockers promptly to STEMI patients without contraindications, especially if a tachyarrhythmia or hypertension is present. *(Level of Evidence: B)*

During the first few hours after the onset of STEMI, beta-blocking agents may diminish myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. In addition, prolongation of diastole caused by a reduction in heart rate may augment perfusion to ischemic myocardium, particularly the subendocardium. As a result, immediate beta-blocker therapy appears to reduce 1) the magnitude of infarction and incidence of associated complications in subjects not receiving concomitant fibrinolytic therapy, 2) the rate of reinfarction in patients receiving fibrinolytic therapy, and 3) the frequency of life-threatening ventricular tachyarrhythmias.

In patients not receiving fibrinolytic therapy, intravenously administered beta-blocking agents exert a modestly favorable influence on infarct size (265). Large early trials suggested a mortality benefit as well. In ISIS-1 (266), more than 16 000 patients with suspected acute MI were enrolled within 12 hours of onset of symptoms; immediate atenolol, 5 to 10 mg IV, followed by oral atenolol, 100 mg daily, reduced 7-day mortality from 4.3% to 3.7% (p less than 0.02; 6 lives saved per 1000 treated). The mortality difference between those receiving and not receiving atenolol was evident by the end of day 1 and was sustained subsequently. In the Metoprolol In Acute Myocardial Infarction (MIAMI) trial (267), more than 5700 subjects with evolving MI were randomly assigned to receive placebo or metoprolol, up to 15 mg IV in 3 divided doses followed by 50 mg orally every 6 hours for 48 hours and then 100 mg twice per day thereafter. Fifteen-day mortality was reduced with metoprolol from 4.9% to 4.3%. As in ISIS-1, the mortality difference between those given placebo and those receiving metoprolol was evident by the end of day 1, after which it was sustained.

In subjects receiving concomitant fibrinolytic therapy, intravenously administered beta-blocking drugs diminish the incidence of subsequent nonfatal reinfarction and recurrent ischemia. In addition, they may reduce mortality if given particularly early (i.e., within 2 hours) after onset of symptoms. In the Thrombolysis In Myocardial Infarction Phase II (TIMI-II) trial (268), in which all patients received IV alteplase, those randomly assigned to receive metoprolol, 15 mg IV, followed by oral metoprolol, 50 mg twice per day for 1 day and then 100 mg twice per day thereafter, had a diminished incidence of subsequent nonfatal reinfarction and recurrent ischemia compared with those begun on oral metoprolol 6 days after the acute event. Among those treated especially early (i.e., within 2 hours of symptom onset), the composite end point, death or reinfarction, occurred less often in those given immediate IV metoprolol than in those who did not receive it.

The benefits of routine early IV use of beta-blockers in the fibrinolytic era have been challenged by 2 later randomized trials of IV beta-blockade (269,270) and by a post hoc analysis of the use of atenolol in the GUSTO-I trial (271). A subsequent systematic review of early beta-blocker therapy in STEMI found no significant reduction in mortality (67). Therefore, data on the early use of intravenous beta-blockade in STEMI are inconclusive, and patterns of use vary.

Beta-blockers should not be administered to patients with STEMI precipitated by cocaine use because of the risk of exacerbating coronary spasm (272). If IV beta-blockade induces an untoward effect, such as atrioventricular (AV) block, excessive bradycardia, or hypotension, the condition is quickly reversed by infusion of a beta-adrenergic agonist (i.e., isoproterenol 1 to 5 mcg/min). The presence of moderate LV failure early in the course of STEMI should preclude the use of early IV beta-blockade until the heart failure has been compensated but is a strong indication for the oral use of beta-blockade before discharge from the hospital.

The following are relative contraindications to beta-blocker therapy: heart rate less than 60 bpm, systolic arterial pressure less than 100 mm Hg, moderate or severe LV failure, signs of peripheral hypoperfusion, shock, PR interval greater than 0.24 second, second- or third-degree AV block, active asthma, or reactive airway disease.

Randomized trials of beta-blocker therapy in patients with STEMI undergoing PCI without fibrinolytic therapy have not been performed. However, it seems reasonable pending further information to extrapolate data from those receiving

another form of revascularization, fibrinolytic therapy, to the PCI population. The more contemporary CAPRICORN (Carvedilol Post-infarct Survival Controlled Evaluation) trial (273), which includes patients undergoing either form of revascularization, confirms the benefits of beta-blocker therapy in patients with transient or sustained postinfarction LV dysfunction.

6.3.1.6. Reperfusion

6.3.1.6.1. General Concepts

Class I

All STEMI patients should undergo rapid evaluation for reperfusion therapy and have a reperfusion strategy implemented promptly after contact with the medical system. *(Level of Evidence: A)*

Although rapid spontaneous reperfusion of the infarct artery may occur, in the majority of patients there is persistent occlusion of the infarct artery in the first 6 to 12 hours while the affected myocardial zone is undergoing necrosis. Prompt and complete restoration of flow in the infarct artery can be achieved by pharmacological means (fibrinolysis), PCI (balloon angioplasty with or without deployment of an intracoronary stent under the support of pharmacological measures to prevent thrombosis), or surgical measures (Figure 3) (24-40). Despite the extensive improvement in intraoperative preservation with cardioplegia and hypothermia and in numerous surgical techniques, it is not logistically possible to provide surgical reperfusion in a timely fashion, and therefore patients with STEMI who are candidates for reperfusion routinely receive either fibrinolysis or a catheter-based treatment.

Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in patients with STEMI is a key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI (24,274,275). As discussed previously (Section 4.1), efforts should be made to shorten the time from recognition of symptoms by the patient to contact with the medical system. All healthcare providers caring for patients with STEMI from the point of entry into the medical system must recognize the need for rapid triage and implementation of care in a fashion analogous to the handling of trauma patients. When considering recommendations for timely reperfusion of patients with STEMI, the Writing Committee reviewed data from clinical trials, focusing particular attention on enrollment criteria for selection of patients for randomization, actual times reported in the trial report rather than simply the allowable window specified in the trial protocol, treatment effect of the reperfusion strategy on individual components of a composite primary end point (e.g., mortality, recurrent nonfatal infarction), ancillary therapies (e.g., antithrombin and antiplatelet agents), and the interface between fibrinolysis and referral for angiography and revascularization. When available, data from registries were also reviewed to assess the generalizability of observations from clinical trials of reperfusion to routine practice. Despite the wealth of reports on reperfusion for STEMI, it is not possible to produce a simple algorithm given the heterogeneity of patient profiles and availability of resources in various clinical settings at various times of day. This section introduces the recommendations for an aggressive attempt to minimize the time from entry into the medical system to implementation of a reperfusion strategy using the concept of medical system goals. More detailed discussion of these goals and the issues to be considered in selecting the type of reperfusion therapy may be found in Section 6.3.1.6.2, followed by a discussion of available resources in Section 6.3.1.6.2.1.

The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI such that door-to-needle (or medical contact–to-needle) time for initiation of fibrinolytic therapy can be achieved within 30 minutes or that door-to-balloon (or medical contact–to-balloon) time for PCI can be kept under 90 minutes. These goals may not be relevant for patients with an appropriate reason for delay, such as uncertainty about the diagnosis (particularly for the use of fibrinolytic therapy), need for evaluation and treatment of other life-threatening conditions (e.g., respiratory failure), or delays associated with the patient's informed choice to have more time to consider the decision. In the absence of such types of circumstances, the emphasis is on having a system in place such that when a patient with STEMI presents for medical care, reperfusion therapy can be provided as soon as possible within these time periods. Because there is not considered to be a threshold effect for the benefit of shorter times to reperfusion, these goals should not be understood as "ideal" times but rather the longest times that should be considered acceptable. Systems that are able to achieve even more rapid times for patients should be encouraged. Also, this goal should not be perceived as an average performance standard but as a goal that an early treatment system in every hospital should seek for every appropriate patient.

A critically important goal of reperfusion is to restore flow in the infarct artery as quickly and as completely as possible, but the ultimate goal of reperfusion in STEMI is to improve myocardial perfusion in the infarct zone. Despite adequate restoration of flow in the epicardial infarct artery, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury (276-278). Microvascular damage occurs as a consequence of downstream embolization of platelet microemboli and thrombi followed by the release of substances from activated platelets that promote occlusion or spasm in the microvasculature. Reperfusion injury results in cellular edema, free radical formation, calcium overload, and acceleration of the apoptotic process. Cytokine activation in the infarct zone leads to neutrophil accumulation and inflammatory mediators that contribute to tissue injury.

Thus, construction of an ideal reperfusion regimen in patients with STEMI not only should focus on the primary means of restoring flow in the epicardial infarct artery (pharmacological or catheter-based) but should also include

adjunctive and ancillary treatments that minimize the amount of microvascular damage and protect the jeopardized myocardial infarct zone that contains cells in various stages of ischemia, necrosis, and apoptosis (279,280). The Writing Committee endorses further research to identify the optimum strategies for achieving these goals.

6.3.1.6.2. SELECTION OF REPERFUSION STRATEGY. The literature provides very strong evidence that among patients with suspected STEMI and without contraindications, the prompt use of reperfusion therapy is associated with improved survival (156). Despite such strong evidence, studies continue to indicate that reperfusion therapy is underutilized and often not administered soon after presentation (281-283). Indecision about the choice of reperfusion therapy should not deter physicians from using these strategies or delay them in administering therapy.

There is controversy about which form of reperfusion therapy is superior in various clinical settings. Part of the uncertainty derives from the continual introduction of new agents, devices, and strategies, which quickly make previous studies less relevant to contemporary practice. With pharmacological reperfusion therapies, there are new agents, dosing regimens, adjunctive treatments, and combined strategies with procedures that are in a continual process of refinement and evaluation. Similarly, with catheter-based approaches, there are new devices, adjunctive therapies, technologies, and combined strategies with medications that are being introduced and evaluated. As a result, the evidence base regarding the best approach to reperfusion therapy is quite dynamic.

Several issues should be considered in selecting the type of reperfusion therapy, as discussed below.

Time From Onset of Symptoms. Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome (284). The efficacy of fibrinolytic agents in lysing thrombus diminishes with the passage of time (279). Fibrinolytic therapy administered within the first 2 hours (especially the first hour) can occasionally abort MI and dramatically reduces mortality (Figure 13) (156,159). The National Heart Attack Alert Working Group (179) recommends that EDs strive to achieve a 30-minute door-to-needle time to minimize treatment delays. Prehospital fibrinolysis reduces treatment delays by up to 1 hour and reduces mortality by 17% (285).

The amount of myocardium at risk, presence of collateral blood flow, and duration of coronary occlusion are major determinants of myocardial infarct size (286-289). In animal models (18), occlusions persisting greater than 30 minutes produce myonecrosis. Reperfusion at 90 minutes salvages approximately half of the myocardium at risk. Myocardial salvage is minimal after 4 to 6 hours of ischemia unless ischemic preconditioning and/or collateral flow have modified the wave front of necrosis.

A time-dependent decrease in efficacy of fibrinolytic therapy may also contribute to the higher mortality rate in patients with longer symptom duration (279). In contrast, the ability to produce a patent infarct artery is much less dependent on symptom duration in patients undergoing PCI. Several reports claim no influence of time delay on mortality rates when PCI is performed after 2 to 3 hours of symptom duration (290,291). One study suggests that time to PCI is only important for patients presenting with shock (292). Another showed that time was associated with outcome in higher-risk but not lower-risk patients (293). Conversely, others have reported increasing mortality rates with increasing door-to-balloon times (294,295). Importantly, after adjustment for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with 1-year mortality in patients undergoing primary PCI for STEMI (relative risk [RR] equals 1.08 for each 30-minute delay from symptom onset to balloon inflation, p equals 0.04) (275,275a). Interestingly, although the CAPTIM (173) and PRAGUE-2 (177) studies reached different conclusions about the overall superiority of PCI over fibrinolysis, important observations were made in the subset of patients presenting very early after the onset of symptoms. In the subset of patients presenting within 3 hours of the onset of symptoms in PRAGUE-2, mortality was equivalent in those treated with streptokinase and those transferred with PCI (177). Patients treated within 2 hours of symptom onset in CAPTIM had improved outcomes with prehospital tissue plasminogen activator (tPA) versus transfer for PCI (176). (See Section 6.3.1.6.2.1.)

It is also possible that time-to-treatment analyses have been confounded by other variables (293,296). First, higher-risk patients report later to the hospital and may respond better to PCI than to fibrinolytic agents. Second, shorter door-to-balloon times may be a surrogate for better quality of care and adherence to treatment guidelines. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology (297) and this Committee both recommend a target medical contact– or door-to-balloon time of less than 90 minutes.

Risk of STEMI. Several models have been developed that assist clinicians in estimating the risk of mortality in patients with STEMI (240-242,298,299). Although these models vary somewhat in the factors loaded into the risk prediction tool and also vary with respect to statistical measures of their discriminative power (e.g., C statistic), all the models provide clinicians with a means to assess the continuum of risk from STEMI. None of the models have been tested prospectively by randomizing patients to a reperfusion strategy based on estimated mortality at presentation. Retrospective analyses do suggest that the absolute difference in mortality at 30 days between PCI and fibrinolysis increases in favor of PCI as the estimated risk of mortality with fibrinolysis increases (300). Conversely, as the estimated mortality benefit with fibrinolysis decreases, the absolute mortality benefit of PCI decreases, with equipoise appearing (i.e., similar 30-day mortality rates) when the estimated mortality with fibrinolysis is approximately 2% to 3% (300).

When the estimated mortality with fibrinolysis is extremely high, as is the case in patients with cardiogenic shock,

Presentation features	Percent of patients dead Fibrinolytic	Control	Stratified statistics O-E	Variance	Chi-square test of odds ratios In different patients categories: Heterogeneity	Trend
ECG						
BBB	18.7 %	23.6 %	-24.5	83.3		
ST elev. anterior	13.2 %	16.9 %	-122	420.6		
ST elev. inferior	7.5 %	8.4 %	-27.1	237.4		
ST elev. other	10.6 %	13.4 %	-42.1	159.6	21.26 on 6 df	
ST depression	15.2 %	13.8 %	12.9	108.7	(P<0.1)	
Other abnormality	5.2 %	5.8 %	-9.6	103.2		
Normal	3.0 %	2.3 %	3.4	12.9		
Hours from onset						
0 - 1	9.5 %	13.0 %	-29.3	83.3		
2 - 3	8.2 %	10.7 %	-100.2	354.8		
4 - 6	9.7 %	11.5 %	-78.5	387.6	9.69 on 4 df	9.55 on 1 df
7 - 12	11.1 %	12.7 %	-51.5	336.7	(P< 0.05)	(2P=0.002)
13 - 24	10.0 %	10.5 %	-11.1	212.6		
Age (years)						
<55	3.4 %	4.6 %	-45.9	155.6		
55-64	7.2 %	8.9 %	-56.3	360.0	8.27 on 3 df	6.58 on 1 df
65-74	13.5 %	16.1 %	-113.7	533.0	(P < 0.05)	(2P=0.01)
75+	24.3 %	25.3 %	-12.6	266.6		
Gender						
Male	8.2 %	10.1 %	-208.1	926.0	1.99 on 1 df	
Female	14.1 %	16.0 %	-62.2	436.8	(NS)	
Systolic BP (mm Hg)						
<100	28.9 %	35.1 %	-38.7	132.2		
100-149	9.6 %	11.5 %	-168.9	850.0	1.31 on 3 df	0.68 on 1 df
150-174	7.5 %	8.7 %	-58.2	290.0	(NS)	(NS)
175+	7.2 %	8.2 %	-10.8	74.1		
Heart rate						
<80	7.2 %	8.5 %	-83.2	454.0		
80-99	9.2 %	11.3 %	-55.8	267.2	0.51 on 2 df	0.31 on 1 df
100+	17.4 %	20.7 %	-51.7	238.6	(NS)	(NS)
Prior MI						
Yes	12.5 %	14.1 %	-43.7	322.4	2.09 on 1 df	
No	8.9 %	10.9 %	-228.5	1001.9	(NS)	
Diabetes						
Yes	13.6 %	17.3 %	-41.4	145.7	1.57 on 1 df	
No	8.7 %	10.2 %	-142.6	830.4	(NS)	
ALL PATIENTS	2820/29315 9.6 %	3357/29285 11.5 %		-269.5	1377.4	18% SD 2 odds reduction 2P < 0.00001

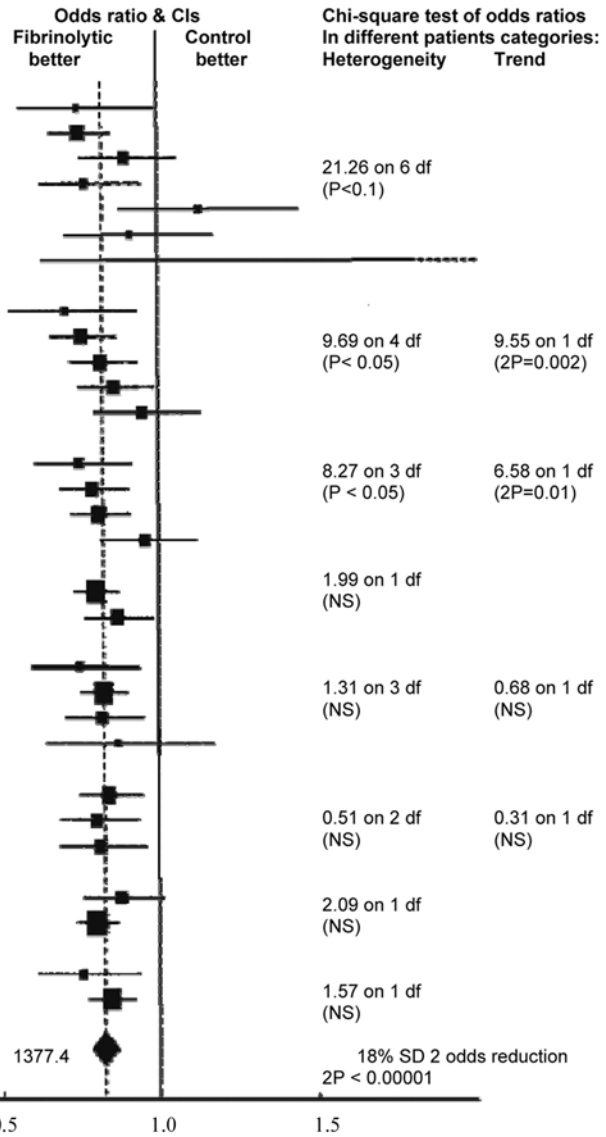


Figure 13. Mortality differences during days 0 through 35 subdivided by presentation features in a collaborative overview of results from nine trials of fibrinolytic therapy. At center absolute mortality rates are shown for fibrinolytic and control groups for each clinical feature at presentation listed at left. The odds ratio of death in fibrinolytic group to that in control group is shown for each subdivision (black square) along with 95% confidence interval (horizontal line). The summary odds ratio at bottom corresponds to an 18% proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1000 patients treated with fibrinolytic agents. O-E indicates observed versus expected ratio; CIs = confidence intervals; ECG = electrocardiogram; BBB = bundle-branch block; ST elev = ST-segment elevation; df = degrees of freedom; BP = blood pressure; MI = myocardial infarction; SD = standard deviation. Reprinted with permission from Elsevier (Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. The Lancet 1994; 343:311-22) (156).

compelling evidence exists that favors a PCI strategy. The SHOCK trial (SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK?) demonstrated that patients with cardiogenic shock have a better 1-year survival if they have undergone early coronary revascularization (184). At 1 year, patients in the early revascularization group had a mortality rate of 53% compared with 66% for the group that had initial medical stabilization followed by no or late revascularization (184,301). Observational data from NRMI suggest superiority of PCI over fibrinolysis for patients with Killip class greater than or equal to II (302).

Risk of Bleeding. Choice of reperfusion therapy is also affected by the patient's risk of bleeding. When both types of reperfusion are available, the higher the patient's risk of bleeding with fibrinolytic therapy, the more strongly the decision should favor PCI. If PCI is unavailable, then the benefit of pharmacological reperfusion therapy should be balanced against the risk. A decision analysis suggested that fibrinolytic therapy should be favored against no reperfusion treatment until the risk of a life-threatening bleed exceeds 4% in older patients who have a risk profile similar to those in the classic randomized trials of fibrinolytic therapy (247).

Risk scores for bleeding after fibrinolytic therapy allow for the calculation of this risk (246). Because they are derived from less restricted populations, the scores that are most generalizable are those derived from observational studies (246).

Time Required for Transport to Skilled PCI Laboratory. The availability of interventional cardiology facilities is a key determinant of whether PCI can be provided. For facilities that can offer PCI, the literature suggests that this approach is superior to pharmacological reperfusion (303). The trials comparing pharmacological and PCI strategies, however, were conducted before the advent of more recent pharmacological and PCI strategies. When a composite end point of death, nonfatal recurrent MI, or stroke is analyzed, much of the superiority of a PCI strategy is driven by a reduction in the rate of nonfatal recurrent MI (Figure 14) (40). The rate of nonfatal recurrent MI can be influenced both by the adjunctive therapy used (Figure 3) (24-40) and by the proportion of patients who are referred for PCI when the initial attempt at fibrinolysis fails or myocardial ischemia recurs after initially successful pharmacological reperfusion (Figure 14) (155).

The experience and location of the PCI laboratory also plays a role in the choice of therapy. The trials were performed in centers with highly experienced teams, and their results may not be generalizable to all PCI laboratories throughout the country. Not all laboratories can provide prompt, high-quality primary PCI. Even centers with interventional cardiology facilities may not be able to provide the staffing required for 24-hour coverage of the catheterization laboratory. Despite staffing availability, the volume of cases in the laboratory may be insufficient for the team to acquire and maintain skills required for rapid PCI reperfusion strategies. A study from NRMI investigated the effect of volume on the outcomes of patients treated with PCI versus pharmacological reperfusion strategies (303). They studied 446 acute-care hospitals, with 112 classified as low-volume (fewer than or equal to 16 procedures), 223 as intermediate-volume (17 to 48 procedures), and 111 as high-volume (49 or more procedures) based on their annual primary angioplasty volume. They reported that patients hospitalized at intermediate- and high-volume centers had lower mortality with PCI reperfusion, whereas in the low-volume centers, there was no significant difference between the 2 reperfusion strategies. In another article from the NRMI investigators, the volume of primary PCI procedures, but not pharmacological treatment, was inversely associated with the mortality rate for patients with STEMI (304).

A decision must be made when a STEMI patient presents to a center without interventional cardiology facilities. Fibrinolytic therapy can generally be provided sooner than primary PCI (Figure 7) (180). As the time delay for performing PCI increases, the mortality benefit associated with expeditiously performed primary PCI over fibrinolysis decreases (305). Compared with a fibrin-specific lytic agent, a PCI strategy may not reduce mortality when a delay greater than 60 minutes is anticipated versus immediate administration of a lytic (Figure 15) (305).

The balance of risk/benefit between the transfer of patients for PCI and more immediate treatment with fibrinolytic therapy remains uncertain. The DANAMI-2 trial (DANish trial in Acute Myocardial Infarction), conducted in Denmark, found that patients treated at facilities without interventional cardiology capabilities had better composite outcomes with transfer for PCI within 2 hours of presentation than with pharmacological reperfusion treatment at the local hospital (306). Whether these results could be replicated elsewhere is not known. An alternative to transfer is for hospitals without on-site cardiac surgery to develop the capability to provide primary mechanical reperfusion therapy. A study by Aversano and colleagues with 11 hospitals in Massachusetts and Maryland suggested that this approach may improve outcomes (307). It can be expected, however, that only a limited number of hospitals could develop such a program, and it has yet to be determined whether a certain volume of cases would be necessary to maintain the effectiveness of the service. The economic implications of expansion of the number of PCI-capable centers that are able to maintain an inventory of the necessary catheters and other devices and provide 24-hour coverage, 7 days per week, deserve further evaluation from the perspectives of individual institutions and the global healthcare delivery system. See additional discussion in Section 6.3.1.6.2.1.

Given the current literature, it is not possible to say definitively that a particular reperfusion approach is superior for all patients, in all clinical settings, at all times of day (173,176,177) (Danchin N; oral presentation, American Heart Association 2003 Annual Scientific Sessions, Orlando, FL, November 2003). The main point is that some type of reperfusion therapy should be selected for all appropriate patients with suspected STEMI. The appropriate and timely use of some reperfusion therapy is likely more important than the choice of therapy, given the current literature and the expanding array of options. Clinical circumstances in which fibrinolytic therapy is generally preferred or an invasive strategy is generally preferred are shown in Table 11.

6.3.1.6.2.1. Available Resources

Class I

STEMI patients presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolysis unless contraindicated. *(Level of Evidence: A)*

The preferred reperfusion therapy for STEMI must take into account the location of the patient, the response time and expertise of the paramedical/ambulance personnel, their relationship to the regional healthcare facility(s), and the availability, capability, and expertise of the medical personnel at the facility. The most recent NRMI data continue to support advantages of primary PCI versus fibrinolysis in high-PCI–volume hospitals but not among those institutions with low volume (fewer than or equal to 16 procedures per year)

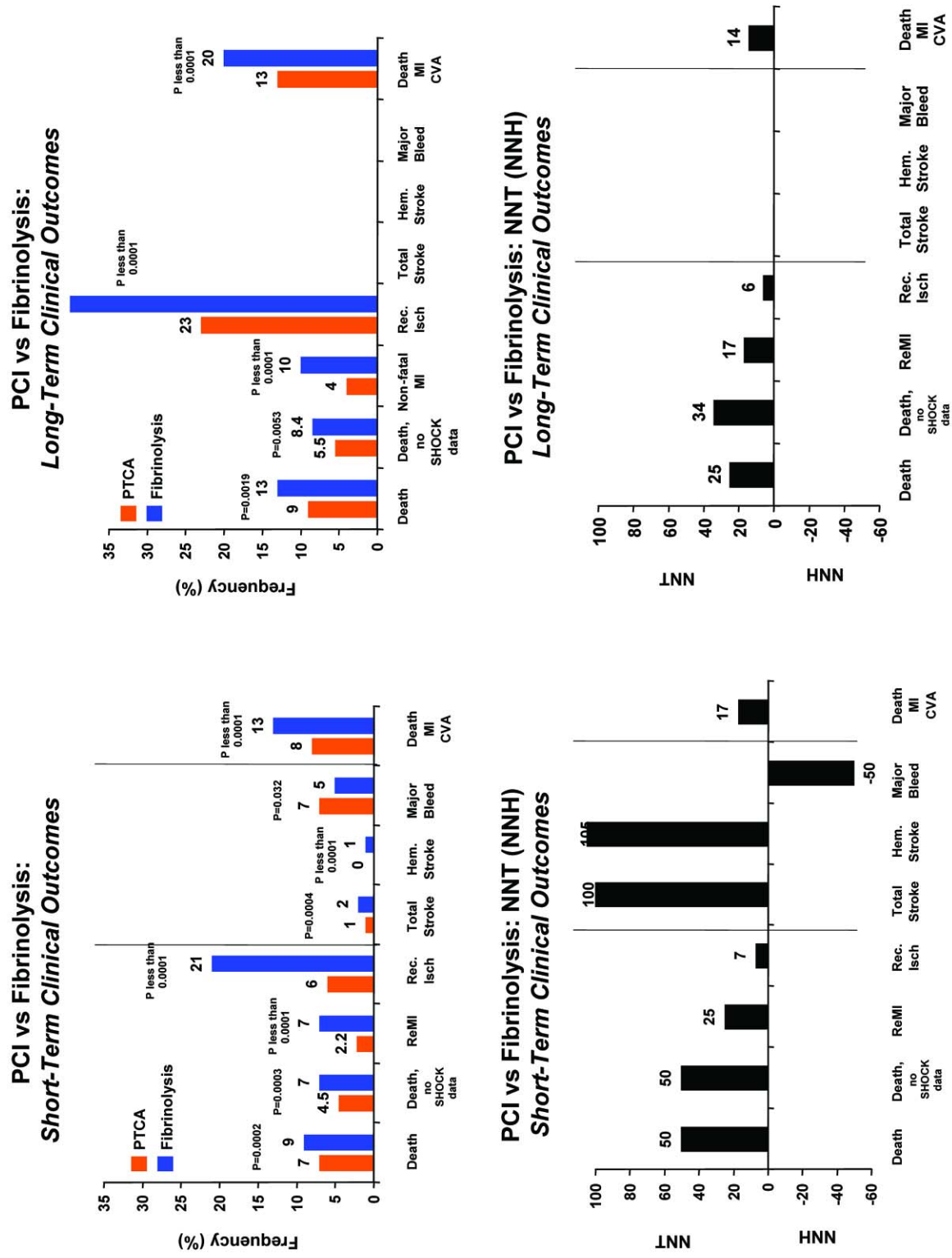


Figure 14. Percutaneous coronary intervention (PCI) versus fibrinolysis for ST-elevation myocardial infarction (STEMI). The short term (4-6 weeks) (top left) and long term (top right) outcomes for the various endpoints shown are plotted for patients with STEMI randomized to percutaneous coronary intervention (PCI) or fibrinolysis for reperfusion in 23 trials (N=7739). Based on the frequency of events for each endpoint in the two treatment groups the number needed to treat (NNT) or number needed to harm (NNH) are shown for the short term (bottom left) and long term (bottom right) outcomes. The magnitude of the treatment differences for death, non-fatal reinfarction, and stroke vary depending on whether PCI is compared with streptokinase or a fibrin-specific lytic. For example, when primary PCI is compared with alteplase (tPA) and the SHOCK trial is excluded, the mortality rate is 5.5% versus 6.7% (OR 0.81, 95% CI 0.64-1.03, P=0.081) (421a). See references (40,421a) for additional discussion. PTCA = percutaneous transluminal coronary angioplasty; ReMI = recurrent MI; Rec. Isch = recurrent ischemia; Hem. Stroke = hemorrhagic stroke; MI = myocardial infarction; and CVA = cerebrovascular accident. Modified with permission from Elsevier (Keeley et al. The Lancet 2003;361:13-20) (40).

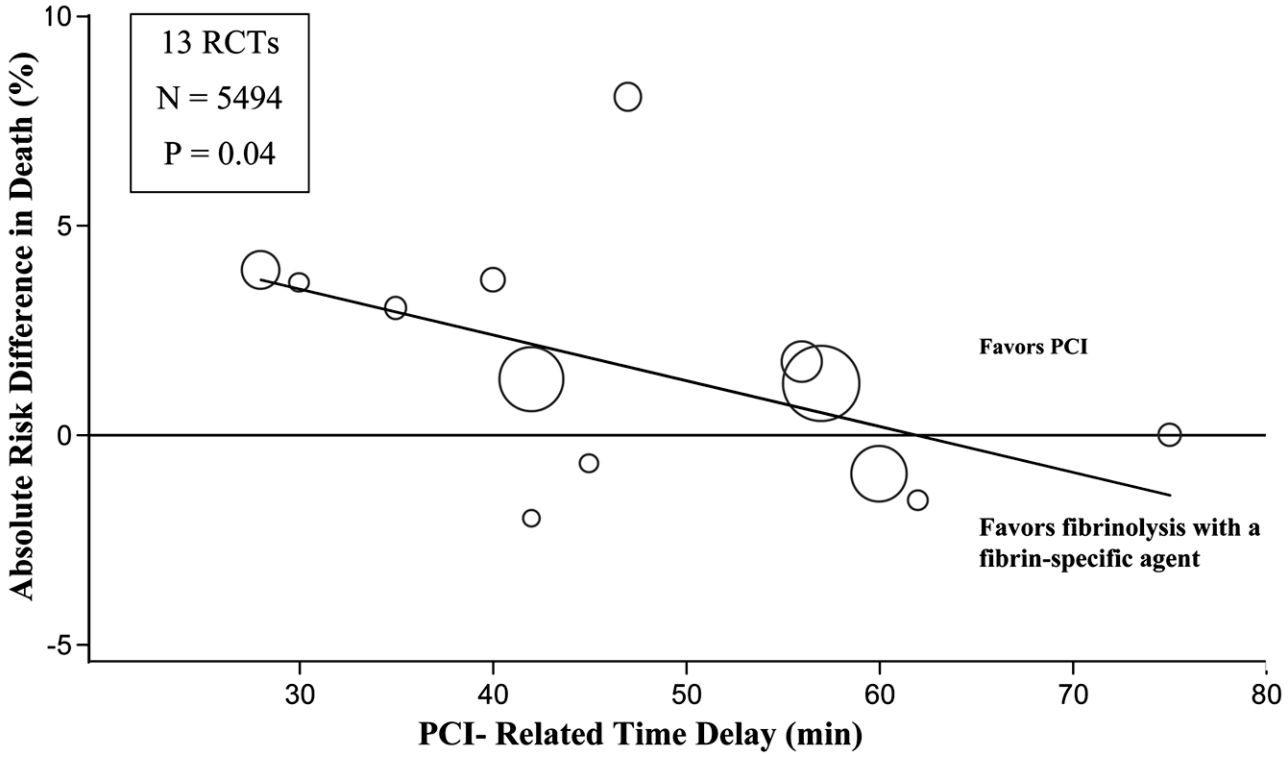


Figure 15. PCI versus lysis with fibrin-specific agents:is timing (almost) everything? RCT = randomized controlled trial; N = Number of patients; PCI = percutaneous coronary intervention. Modified from Nallamothu and Bates. Am J Cardiol 2003;92:824-6 (305). Copyright 2003, with permission from Excerpta Medica, Inc.

Table 11. Assessment of Reperfusion Options for Patients with STEMI

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 for either strategy

Fibrinolysis is generally preferred if (See Section 6.3.1.6.3.1):

- *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 (See Section 6.3.1.6.4.2):

- *Skilled PCI lab available with surgical backup* †‡
  - 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*

STEMI = ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; ICH = intracranial hemorrhage.
*Applies to fibrin-specific agents (See Figure 15).
†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.

(303). Approximately 20% of US hospitals have cardiac catheterization laboratories; and less than that number have the capacity for primary PCI. The C-PORT study (Atlantic Cardiovascular Patient Outcomes Research Team), which randomized 451 fibrinolysis-eligible patients with STEMI treated in 11 community hospitals with diagnostic catheterization but not onsite PCI facilities, is of interest. Patients were randomized within 12 hours of symptom onset to an accelerated alteplase regimen (median door-to-lytic time was 46 minutes) versus primary PCI (median door-to-balloon time 101.5 minutes). At 6 months, the incidence of death, re-MI, and stroke was 12.4% for PCI and 19.9% for fibrinolytic therapy (p equals 0.03). Because only 18% of the intended sample size was actually enrolled, this study is significantly underpowered, and its conclusion can only be hypothesis-generating rather than definitive (307). Importantly, most C-PORT patients were randomized between 0800 and 1600 hours, an experience consistent with NRMI data. The NRMI report also demonstrated a substantially longer door-to-balloon time when patients with STEMI undergo direct PCI outside of daylight hours (308). The Zwolle group evaluated 1702 consecutive patients and found that the 47% of patients who presented outside "routine duty hours" (i.e., 1800 to 0800 hours) had a higher rate of both PCI failure and 30-day mortality than those within the 0800 to 1800 period (6.9% and 4.2% versus 3.8% and 1.9%, respectively; p less than 0.01) (309). The reasons for these differences are unclear but could relate to both patient and process-of-care factors, including variations in both cognitive function and manual dexterity in sleep-deprived healthcare providers (308,310).

Two studies germane to STEMI care and resource utilization are noteworthy. The first, CAPTIM, a comparison of angioplasty and prehospital fibrinolysis (accelerated alteplase) in STEMI, fell short of its planned 1200-patient enrollment, and hence was underpowered (173). Eight hundred forty patients were randomized to prehospital fibrinolysis versus primary PCI. The primary end point was the composite of all-cause mortality, nonfatal recurrent MI, and nonfatal disabling stroke at 30 days, which occurred in 8.2% of patients assigned fibrinolytic therapy and 6.2% of patients assigned to PCI (p not significant [NS]). The components for death, reinfarction, and disabling stroke were 3.8%, 3.7%, and 1.0% for fibrinolytic therapy and 4.8%, 1.7%, and 0% for PCI. Unlike C-PORT, this trial liberally used rescue angioplasty (28%), which probably accounts for the relatively low reinfarction rate in the lytic-treated group. A subsequent analysis from CAPTIM of the 55% of patients treated within 2 hours of symptom onset revealed a mortality trend in favor of prehospital fibrinolysis versus primary PCI (2.2% versus 5.7%, p equals 0.058), whereas those patients treated beyond 2 hours had a 5.9% versus 3.7% (p equals 0.47) 30-day mortality rate, respectively (176). Interestingly, there was a significant reduction in the frequency of cardiogenic shock for patients treated within 2 hours with prehospital fibrinolysis (1.3% versus 5.3%, p equals 0.032), whereas the frequency of this event after 2 hours was similar (i.e., 3.9% versus 4.4%, respectively) (176).

The DANAMI-2 study, which compared primary PCI versus accelerated alteplase, enrolled 1572 patients versus the 2000 patients planned (306). Patients were eligible if they had a sum of greater than 0.4 mV of ST elevation in 2 contiguous leads on their presenting ECG within 12 hours of symptom onset; however, patient enrollment consisted of 37% of those screened, and patients deemed to be at high risk during ambulance transport were excluded (306). Twenty-nine hospitals, of which 5 conducted primary PCI and were located a mean of 35 miles from referring hospitals (maximum 95 miles), participated. The median door-to-needle time for patients randomized to fibrinolysis was approximately 50 minutes for patients presenting either to a community (referral) hospital or an invasive center. For patients who presented to a community hospital (where 1129 patients were enrolled), the time from initial presentation to balloon inflation at an invasive center was 108 minutes; the door-to-balloon time was 93 minutes for patients presenting to an invasive center and randomized to PCI. The primary composite end point of death, reinfarction, and stroke through 30 days occurred in 14.2% of the fibrinolysis-treated patients and 8.5% of the PCI-treated patients (p less than 0.001). The individual end-point components of death, reinfarction, and stroke occurred in 7.8%, 6.3%, and 2.0% of the fibrinolysis-treated patients and 6.6%, 1.6%, and 1.1% of the PCI-treated patients, respectively. In addition to the exclusion of high-risk patients for transport, some caveats in DANAMI-2 are noteworthy: 1) The antithrombotic dosing regimen was in excess of ACC/AHA guidelines. 2) The protocol specified that repeat fibrinolysis was to be used for failed reperfusion, reinfarction, and recurrent ST-elevation ischemia; this strategy was used in 26 patients within 12 hours after randomization, and only 1.9% underwent rescue PCI. 3) Patients with prior stroke were included, and an imbalance in this baseline characteristic was present, (i.e., 4.0% for fibrinolysis versus 2.7% for PCI ([1-sided p equals 0.06]). 4) The difference in reinfarction rates between the 2 groups was likely exaggerated by the exclusion of those patients associated with invasive procedures (311).

Hence, on the basis of the data, patients with STEMI presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolysis unless contraindicated. (See Sections 6.3.1.6.4.2, Primary PCI, and 6.3.1.6.4.2.4, Interhospital Transfer for Primary PCI.)

6.3.1.6.3. PHARMACOLOGICAL REPERFUSION. *RATIONALE FOR FIBRINOLYTIC THERAPY*. Although the clinical features of coronary obstruction were described nearly a century ago (312,313), thrombotic obstruction of the infarct artery as a cause of STEMI was not proven until 1980 (20). The benefits of fibrinolytic therapy are maximal when there is prompt, adequate restoration of flow in the epicardial infarct artery and perfusion of the myocardium in the infarct zone. Controlled clinical trials have demonstrated the potential for

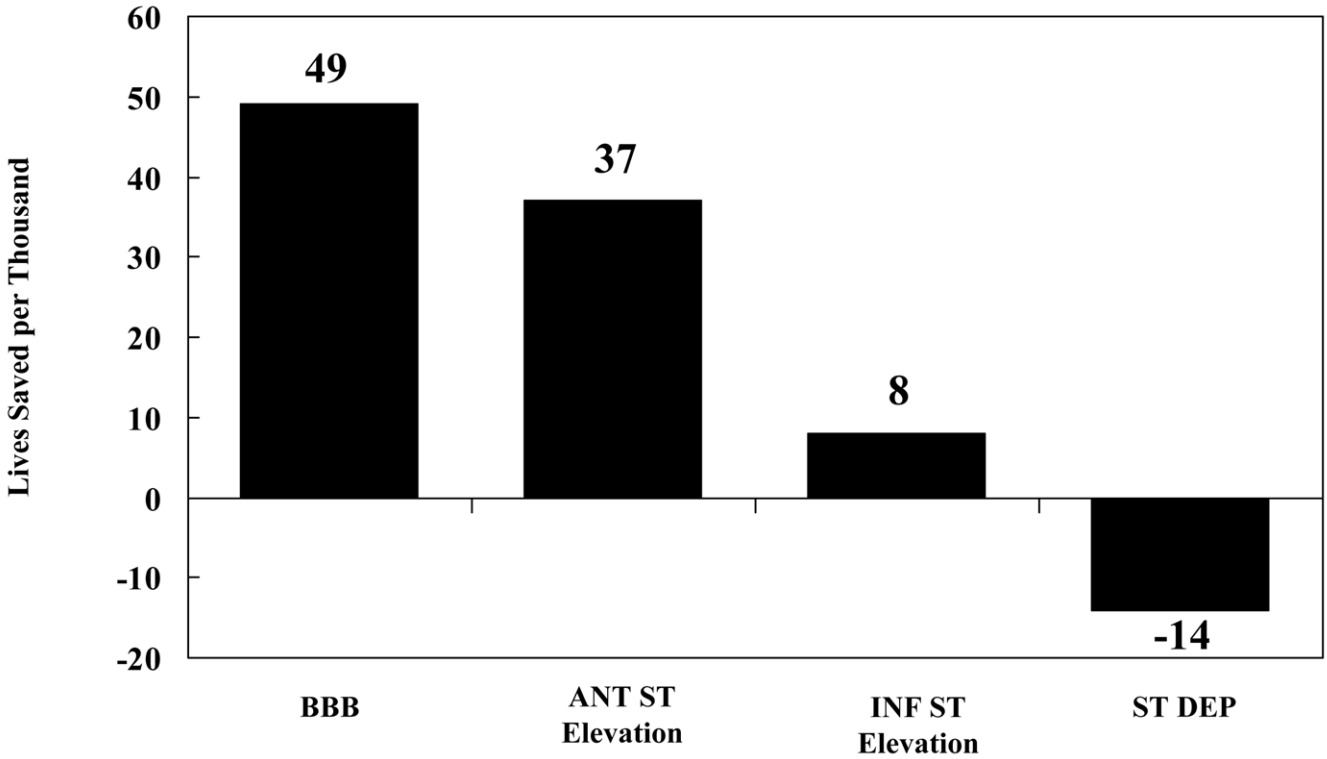


Figure 16. Effect of fibrinolytic therapy on mortality according to admission electrocardiogram. Patients with bundle-branch block (BBB) and anterior ST-segment elevation (ANT ST Elevation) derive the most benefit from fibrinolytic therapy. Effects in patients with inferior ST-segment elevation (INF ST Elevation) are much less, while patients with ST-segment depression (ST DEP) do not benefit. Reprinted with permission from Elsevier (Fibrinolytic Therapy Trialists' Collaborative Group. The Lancet 1994;343:311-22) (156).

functional, clinical, and mortality benefits only if fibrinolytic therapy is given within 12 hours. (See additional discussion on the use of antithrombins and antiplatelet agents as ancillary therapy in Sections 6.3.1.6.8.1 and 6.3.1.6.8.2.)

The reduction in mortality with fibrinolytic therapy is present regardless of sex, presence of diabetes, blood pressure (if less than 180 mm Hg systolic) (246,314), heart rate, or history of previous MI (156). The mortality benefit is greater in the setting of anterior STEMI, diabetes, low blood pressure, (less than 100 mm Hg systolic) or high heart rate (greater than 100 bpm) (Figure 13) (156). The earlier therapy begins, the better the outcome, with the greatest benefit decidedly occurring when therapy is given within the first 3 hours. Benefit occurs, however, up to at least 12 hours from the onset of symptoms. The absolute benefit is less with inferior STEMI, except for the subgroup with associated RV infarction or anterior ST-segment depression indicative of a greater territory at risk (Figure 16) (156).

6.3.1.6.3.1. 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 2 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 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 2 contiguous precordial leads or at least 2 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)***

Table 12. Contraindications and Cautions for Fibrinolysis in ST-Elevation Myocardial Infarction*

Absolute contraindications
Any prior ICH
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 months
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)†
History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications
Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (within less than 3 weeks)
Recent (within 2-4 weeks) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

ICH = intracranial hemorrhage; SBP = systolic blood pressure; DBP = diastolic blood pressure; CPR = cardiopulmonary resuscitation; INR = international normalized ratio; MI = myocardial infarction.

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.

†Could be an absolute contraindication in low-risk patients with MI (see Section 6.3.1.6.3.2).

Because the benefit of fibrinolytic therapy is directly related to the time from symptom onset, treatment benefit is maximized by the earliest possible application of therapy. The constellation of clinical features that must be present (although not necessarily at the same time) to serve as an indication for fibrinolysis includes symptoms of myocardial ischemia and ST elevation greater than 0.1 mV, in 2 contiguous leads, or new or presumably new LBBB on the presenting ECG (156,315). In the very early phase of STEMI, giant hyperacute T waves may precede ST elevation (316). True posterior MI may be manifested by tall R waves in the right precordial leads and ST-segment depression in leads V_1 through V_4, especially when T waves are upright (317). Repeat ECGs and incorporation of additional leads such as V_7 through V_9 are more specific for the detection of posterior infarction (225). Patients with LBBB or anterior ST elevation are at greater inherent risk from MI and achieve greater benefit with fibrinolytic therapy. Additional valuable information may be garnered from concurrent echocardiography to identify the location and extent of regional wall-motion abnormalities. Patients with inferior MI and ST elevation in V_1, V_4R, or both are more likely to have concomitant RV infarction (318). Attainment of additional ECG leads (right sided and/or posterior) or an echocardiogram may help clarify the location and extent of infarction and anticipated risk of complications, but it is important that acquisition of such ancillary information not interfere with the strategy of providing timely reperfusion in patients with STEMI (319).

6.3.1.6.3.2. Contraindications/Cautions

Class I

1. **Healthcare providers should ascertain whether the patient has neurological contraindications to fibrinolytic therapy, including: any history of intracranial hemorrhage or significant closed head or facial trauma within the past 3 months, uncontrolled hypertension, or ischemic stroke within the past 3 months. (See Table 12 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 Table 11 for further management considerations.)** ***(Level of Evidence: A)***

A detailed list of contraindications and cautions for the use of fibrinolytic therapy is shown in Table 12. Specific neurological considerations are addressed below.

Hemorrhage represents the most important risk of fibrinolytic therapy, especially ICH, which may be fatal in half to two thirds of patients. There is both legitimate concern and confusion surrounding the issue of whether fibrinolytic therapy should be contraindicated in patients with a history of prior cerebrovascular disease (2,320-322). The 1996 ACC/AHA Guidelines for the Management of Acute Myocardial Infarction (2) stated that "Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 year" was a contraindication to use of thrombolytic therapy and that "...history of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications" was a caution/relative contraindication. After the first 627 patients were enrolled in TIMI-II (320), a number of protocol changes were made: the dose of tPA was reduced from 150 to 100 mg, use of 80 mg of aspirin was postponed for 24 hours, patients who had a history of stroke or intermittent cerebral ischemic attacks were excluded, and patients with blood pressures greater than or equal to 180 mm Hg systolic or greater than or equal to 110 mm Hg diastolic were excluded. The reduction of ICH frequency by the exclusion of patients with any history of cerebrovascular disease was likely confounded by the influence of the other 3 protocol changes. The basis for the 1996 recommendation for a time frame of 1 year for ischemic stroke as a contraindication to coronary fibrinolysis was a consensus opinion without specific supporting data.

In subsequent trials (26-31,33,323,324), the use of prior TIA or stroke as an exclusion criterion has varied: stroke within 2 years (30), stroke within 6 months (323), TIA within 6 months/any history of stroke (33), any stroke (26,27,324), and any history of prior TIA or stroke

(28,29,31) have each been used as exclusion criteria. In some studies, the frequency of ICH in patients older than 75 years ranged from 0.5% with streptokinase and heparin (33) to 2.5% with reteplase (26). Giugliano et al. (325) showed that the higher ICH frequencies with lanoteplase or tenecteplase may be explained in part by the effect of the UFH (InTIME-2 [Intravenous NPA for the Treatment of Infarcting Myocardium Early] equals 1.12%, InTIME-IIb equals 0.50%) and dose of the UFH infusion (ASSENT-1 and TIMI-10B: higher heparin dose equals 1.83%, lower heparin dose equals 0.74%). (See discussion on the use of LMWH in the elderly in Section 6.3.1.6.8.1.2.) In the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) registry (326), previous stroke within 3 months was the strongest predictor of stroke (OR equals 9.3, 95% CI 6.0 to 14.2) after STEMI. On the basis of these data, it appears that the effect of prior stroke/TIA per se on the frequency of ICH after fibrinolysis may be influenced by a number of factors. However, in patients with STEMI with prior ischemic stroke and other ICH risk factors who have a substantial risk for ICH, another reperfusion strategy should be pursued. Additional contraindications to fibrinolytic therapy include a recent history of significant closed head or facial trauma (327).

Estimation of risk of ICH. Several models have been developed for estimating the risk of ICH after fibrinolysis (246,328-330). These models incorporate baseline demographic features of the patient and also illustrate the impact of certain therapeutic decisions (e.g., selection of streptokinase versus tPA; dose of tPA used) (Table 13) (29,246,329,330). Streptokinase without heparin is the regimen associated with the lowest ICH rates (Figure 17) (29,246,329,330).

6.3.1.6.3.3. Effect on Mortality

Efficacy of intravenous fibrinolytic therapy in STEMI. It has now been well established that fibrinolytic therapy provides a survival benefit for patients with STEMI, based on large, well-controlled clinical trials (157,261,331,332). The mechanisms of benefit, which may have different time dependencies, include salvage of myocardium with reduced infarct size, favorable effect on infarct healing and myocardial remodeling, and reduced electrical heterogeneity and potential for life-threatening ventricular arrhythmia (333). An overview from 9 trials of fibrinolytic therapy (versus control) for STEMI has shown a highly significant 18% relative reduction in 35-day mortality (9.6% fibrinolysis versus 11.5% control), which corresponds to a reduction of 18 deaths per 1000 patients treated when data from all patient groups are pooled (156). In patients with ST elevation, a relative mortality reduction of 21% occurred. This survival benefit is maintained over the long term (up to 10 years) (334,335). Mortality reduction from fibrinolytic therapy is greatest within the first hour after symptom onset; thereafter, a decline in benefit of approximately 1.6 lives per 1000 patients treated is seen per 1-hour delay. Additionally, patients with presumed new LBBB, anterior infarction, and the greatest area of risk, as exemplified by the number of ECG leads affected and the extent of ST deviation, derived maximal benefit from fibrinolytic therapy (Figure 16) (156,336).

Elderly patients. Although the elderly constitute a minority of the general population, they are the fastest-growing segment of the population and account for the majority of patients presenting with MI and a disproportionately high component of death from MI (46,213,338). In persons older than 75 years, the overall risk of mortality from MI is high with and without therapy. Although the proportionate reduction in mortality for patients older than 75 years treated within 12 hours with ST elevation or LBBB is somewhat less for patients less than or equal to 75 years, the absolute number of lives saved per 1000 patients treated is actually greater (i.e., 34 lives saved per 1000 patients treated versus 28 for those less than 75 years) (339).

Registry observations from the Cooperative Cardiovascular Project (CCP) database by Thiemann and colleagues of 2673 patients between the age of 75 and 86 years suggested that the 1607 patients receiving fibrinolytics had a lower 30-day survival than those not treated with this therapy (340). Some caution in the interpretation of these observational data is appropriate because 1) a reversal of this effect toward benefit was seen in women between the ages of 65 and 75 years derived from a larger sample, and 2) a substantial proportion of the patients possessed conventional clinical trial fibrinolytic exclusion criteria (i.e., 11.8% had systolic blood pressure greater than 180 mm Hg, 18% had a history of recent trauma or a remote history of peptic ulcer or internal bleeding, and 6.9% had a history of stroke). Twice as many patients receiving fibrinolysis (i.e., 2.2% versus 0.9%) had CPR before arrival as opposed to those without fibrinolysis (340). In contrast to the CCP study by Thiemann et al., another CCP analysis in the elderly by Berger et al. indicated that both fibrinolytic therapy and primary angioplasty were associated with a survival benefit at 1 year compared with patients receiving neither (341). Data from the Swedish National Register on the use of fibrinolysis in 6891 patients 75 years and older with first registry-recorded STEMI also confirm a 13% adjusted relative risk reduction (95% CI 0.80 to 0.94; p equals 0.001; absolute risk reduction 4%) in the composite of mortality and cerebral bleeding after 1 year (Figure 18) (342).

6.3.1.6.3.4. Effect on LV Function

Early reperfusion of ischemic myocardium within the risk region of an occluded infarct-related artery interrupts the wave front of necrosis (18), reduces ultimate infarct size, preserves regional and global ventricular function, and improves survival. Clinical evidence for this paradigm was inconclusive until the GUSTO-I angiographic trial (343-348). Global LV ejection fraction (LVEF), a load-dependent measurement, is an imperfect surrogate for infarct size. Compensatory remote-segment hyperkinesis, the important

Table 13. Models for Estimating Risk of ICH

Risk Factor*	Model		
	Simoons et al (329)	**CCP (246)**	**InTIME-2 (29)**
Age, y	Greater than 65 = 1 point	75 or greater = 1 point	75 or greater = 1 point
Weight	70 kg or less = 1 point	65 kg or less (women) = 1 point 80 kg or less (men) = 1 point	67 kg or less = 1 point
Hypertension on admission	SBP: 170 mm Hg or greater = 1 point DBP: 95 mm Hg or greater = 1 point Both SBP and DBP above limits = 1 point	SBP: 160 mm Hg or greater = 1 point 170 mm Hg or greater = 1 point	SBP: 160 mm Hg or greater = 1 point 170 mm Hg or greater = 1 point
Treatment assignment			
rtPA	1 point	1 point	–
nPA	–	–	1 point
Female	–	1 point	–
Black race	–	1 point	1 point
Prior stroke	–	1 point	1 point
Prior nifedipine use	–	–	1 point
Excessive anticoagulation	–	1 point	–

ICH = intracranial hemorrhage; CCP = Cooperative Cardiovascular Project; InTIME-2 = Intravenous nPA for treatment of Infracting Myocardium Early-2; SBP = systolic blood pressure; DBP = diastolic blood pressure; rtPA = recombinant alteplase; nPA = lanoteplase.
*The sum of the points for each of the models is used for interpretation of the graphs shown in Figure 17.

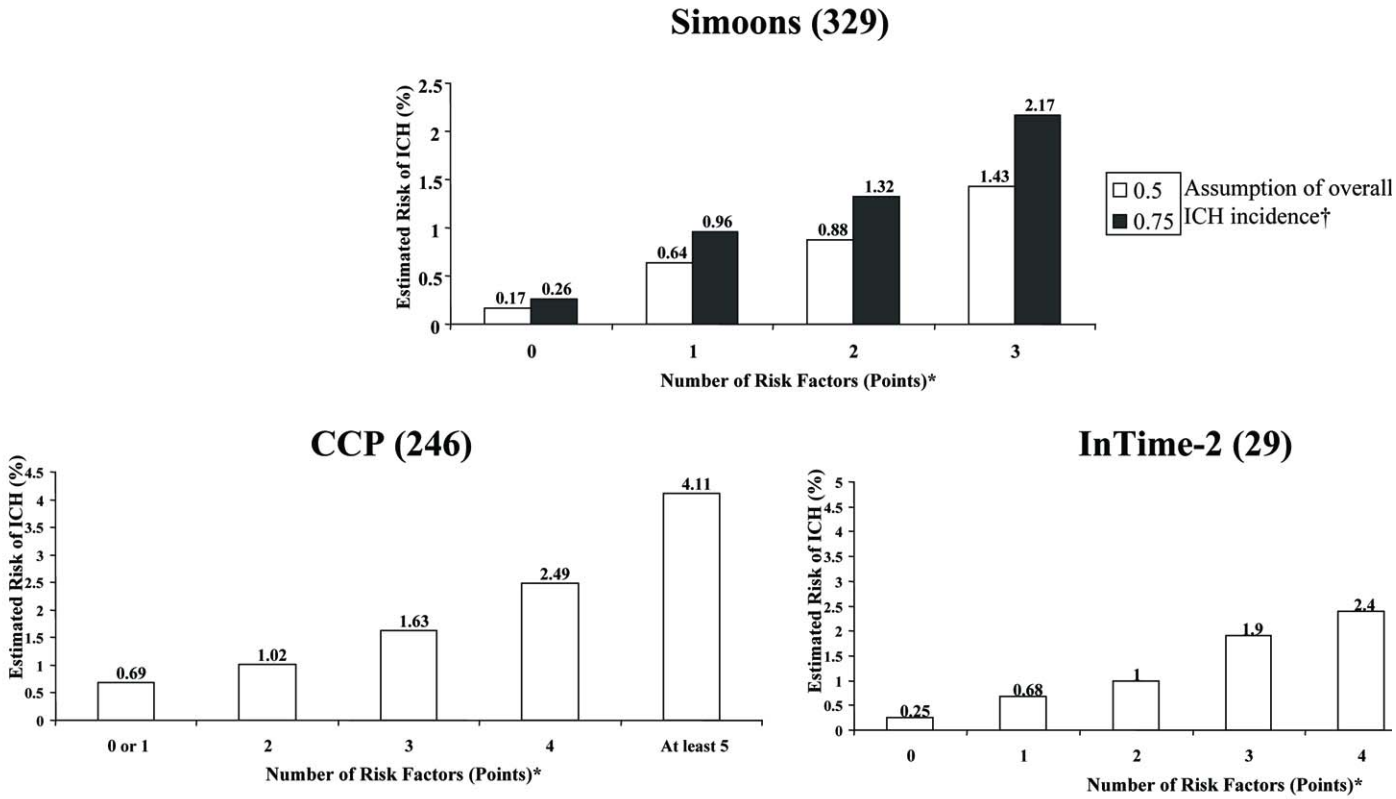


Figure 17. Estimation of risk of ICH with fibrinolysis. ICH = intracranial hemorrhage; CCP = Cooperative Cardiovascular Project; InTIME-2 = Intravenous nPA for treatment of Infracting Myocardium Early-2; *The number of risk factors is the sum of the points based on the criteria shown in Table 13. †If the overall incidence of ICH is assumed to be 0.75%, patients without risk factors who receive streptokinase have a 0.26% probability of ICH. The risk is 0.96%, 1.32%, and 2.17% in patients with 1, 2, or 3 risk factors, respectively. See Simoons et al. (329) for further discussion.

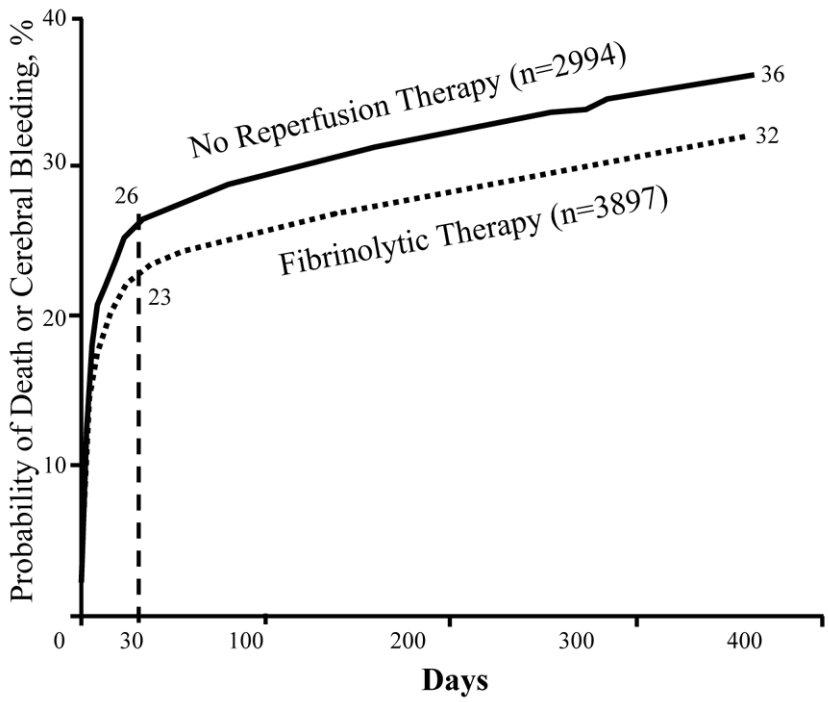


Figure 18. Adjusted probability of death or cerebral bleeding in relation to fibrinolytic therapy in patients with ST-elevation myocardial infarction (STEMI) who were 75 years or older (dotted line) versus that among patients with STEMI not receiving fibrinolysis (solid line). At 30 days and 1 year this was 23% and 32% versus 26% and 36%, respectively. Modified with permission from Stenestrand and Wallentin. Arch Intern Med 2003;163:965-71. Copyrighted © 2003, American Medical Association. All rights reserved (342).

prognostic effect of ventricular dilation, and the potential effects of a patent infarct artery independent of myocardial salvage confound the relationship between early reperfusion, global LV function, and survival. Poor perfusion at the myocardial cellular level due to microvascular obstruction further confounds the relationship between early reflow in the epicardial coronary artery, wall-motion improvement, and survival. In patients with TIMI 3 flow, those with abnormal myocardial tissue perfusion have worse LV function and survival than those with normal perfusion. Myocardial blush on angiography, contrast perfusion on echocardiography, and prompt complete resolution of ST elevation are measures of tissue perfusion. Poor perfusion at the myocardial cellular level is associated with increased morbidity and mortality. However, the mechanism by which poor tissue perfusion confers an adverse prognosis is not clear. Evidence of poor tissue perfusion may be the result of extensive transmural infarction with tissue edema and increased microvascular resistance (349). Alternatively, poor microvascular flow may result from distal embolization of atherothrombotic debris and hence be a target for therapeutic interventions. Flow in the infarct artery before PCI is associated with smaller infarct size and better outcome. Infarct size can be measured with SPECT sestamibi imaging (350), and this has been done in more than a dozen randomized trials.

6.3.1.6.3.5. 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)***

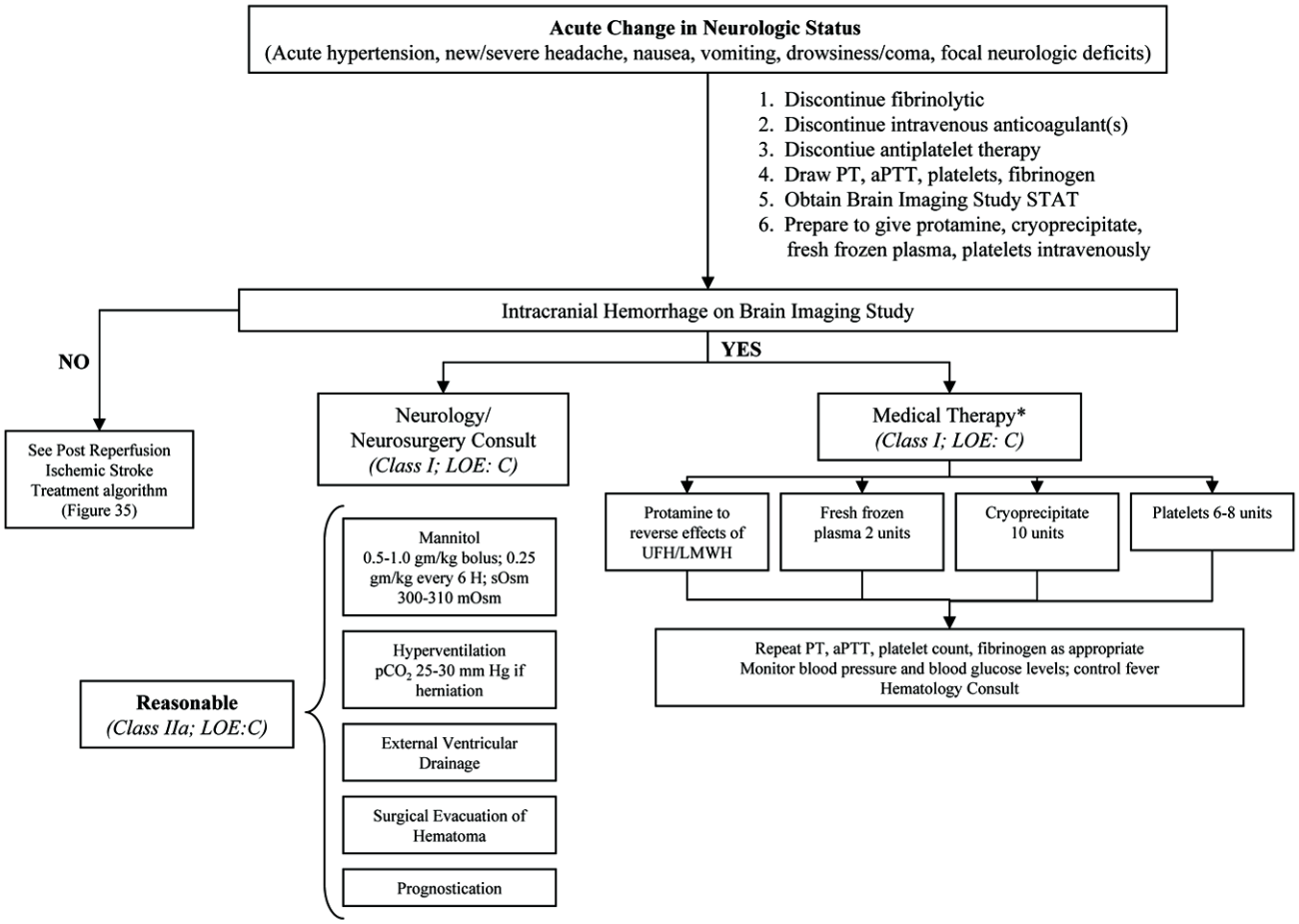


Figure 19. Algorithm for evaluation of intracranial hemorrhage complicating fibrinolytic therapy for ST-elevation myocardial infarction. PT = prothrombin time; aPTT = activated partial thromboplastin time; LOE = level of evidence; H = hours; sOsm = serum osmolality; mOsm = milliosmoles; UFH = unfractionated heparin; LMWH = low-molecular weight heparin. *As dictated by clinical circumstances (see Section 6.3.1.6.3.5). Modified with permission from NINDS rt-PA Stroke Study Group. Stroke 1997;28:1530-40 (370).

Hemorrhagic complications of fibrinolytic therapy primarily include ICH and other moderate or severe bleeding that may or may not require transfusion. The slight but definite excess risk of ICH occurs predominantly within the first day of therapy (156). Summaries of the incidence of ICH with various pharmacological reperfusion regimens are shown in Table 14 (26-31,33,158,261,320,322,324,331,351-369).

ICH may refer to parenchymal hemorrhage (PH), intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma, and epidural hematoma. Between 65% and 77% of ICHs occur within 24 hours of initiation of treatment, up to 77% occur at lobar/subcortical lobar sites, 15% to 33% are multiple PHs, and up to 15% are combined PH and subdural hematoma. Typical presenting features include an acute change in level of consciousness, unifocal or multifocal neurological signs, coma, headache, nausea, vomiting, and seizures, at times with acute hypertension. In many cases, onset is catastrophic and rapidly fatal.

Management of suspected ICH. An algorithm for the management of ICH in the STEMI setting is provided in Figure 19 (370,371). Any change in neurological function, particularly in the first 24 hours after treatment, should be regarded as strongly indicative of PH/intraventricular hemorrhage/subarachnoid hemorrhage/subdural hematoma/epidural hematoma until proven otherwise. Fibrinolytic, anticoagulant, antiplatelet, and combined therapies should be discontinued as soon as symptoms and signs are recognized. An emergency CT scan should be performed as soon as possible to identify the specific type of hemorrhagic complication and to measure the volume of hematoma (372,373). It is useful to document the severity of the coagulopathy, although emergency patient management should not await the results of laboratory testing. Immediate measures to reduce intracranial pressure are reasonable and include mannitol infusion, elevation of the head of the bed to 30 degrees, endotracheal intubation, and hyperventilation to achieve a pCO_2 of 25 to 30 mm Hg. Early involvement of neurologists, neurosurgeons, and hematologists will optimize treatment decisions.

Once PH, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma, or epidural hematoma is documented, the patient should be given 10 U of cryoprecipitate, which will increase the fibrinogen level by approximately 0.70 grams per liter and the factor VIII level by approximately 30% in a 70-kg adult. Fresh frozen plasma can be used as a source of factors V and VIII and as a volume

Table 14. Stroke Complications in Large Comparative Acute ST-Elevation Myocardial Infarction Intravenous Fibrinolysis Trials

Study (References)	No. of Strokes/ No. of Patients Enrolled	% Stroke*	Stroke Subtypes, n (%) ICH	CI	NS	SDH
Fibrinolytics with/without SC/IV UFH						
Streptokinase[33,261,322,324,351-359]						
Subtotal	785/75 221	0.90	258 (33)	316 (40)	205 (26)	16 (1)
Percent of all patients			0.34	0.42	0.27	0.02
rtPA[26-29,320,322,331,353-355,357,359-366]						
Subtotal	1117/74 663	1.50	515 (46)	459 (41)	137 (12)	14 (1)
Percent of all patients			0.69	0.61	0.18	0.01
APSAC[357]						
Subtotal	172/13 599	1.26	54 (31)	67 (39)	12 (7)	16 (9)
Percent of all patients			0.40	0.65	0.12	0.15
Accelerated rtPA plus reduced streptokinase[322]						
Subtotal	170/10 374	1.64	84 (49)	67 (39)	12 (7)	16 (9)
Percent of all patients			0.81	0.65	0.12	0.15
r-scuPA[367]						
Subtotal	15/1698	0.88	8 (53)	7 (47	—-	—-
Percent of all patients			0.47	0.41	—-	—-
Reteplase (r-PA)[26,30,324]						
Subtotal	276/21 482	1.28	164 (59)	92 (33)	20 (8)	—-
Percent of all patients			0.76	0.43	0.09	—-
Tenecteplase[28,31,158]						
Subtotal	193/11 320	1.70	106 (55)	72 (40)†	12 (6)†	—-
Percent of all patients		0.93	0.69	0.11	—-	
Lanoteplase (nPA)[29]						
Subtotal	188/10 038	1.86	112 (60)	76 (40)	—-	—-
Percent of all patients			1.12	0.75	—-	—-
Grand total	2916/218 395	1.34	1301 (45)	1134 (39)	459 (16)	46 (2)
Percent of all patients			0.59	0.52	0.21	0.02
Fibrinolytics with direct thrombin inhibitors[33,359,368]						
Total	124/9308	1.3	65 (52)	44 (35)	15 (13)	—
Percent of all patients			0.7	0.47	0.16	—
Reduced-dose fibrinolytics with GP IIb/IIIa inhibitors[30,31,369]						
Total	112/10 628	1.08	72 (64)	29 (26)	11 (10)	—
Percent of all patients			0.68	0.27	0.13	—
Fibrinolytics with LMWH[31,158]						
Total	57/2858	2.0	36 (63)	12 (36)†	3 (9)†	—
Percent of all patients			1.3	0.59	0.1	—

No. = number of patients with specific stroke subtypes in each study; ICH = definite intracerebral/intracranial hemorrhage; CI = definite ischemic cerebral infarction with/without hemorrhagic transformation; NS = stroke subtype unspecified or "probably" ischemic infarction or "probable" ICH; SDH = subdural hematoma; SC = subcutaneous; IV = intravenous; UFH = unfractionated heparin; rtPA = recombinant alteplase; APSAC = anistreplase; r-scuPA = recombinant single-chain urokinase plasminogen activator; LMWH = low-molecular weight heparin.

expander. In patients who are receiving UFH, 1 mg of protamine for every 100 U of UFH given in the preceding 4 hours may be administered. If the bleeding time is abnormal, infusion of 6 to 8 U of platelets is indicated. In rare cases, antifibrinolytic agents, such as epsilon-aminocaproic acid, may be necessary (374). These replacement/reversal therapies may theoretically be accompanied by reocclusion of the infarct-related artery. Control of blood pressure and blood glucose levels may require a compromise between competing cardiologic and neurological concerns. The decision to use various measures to reduce increased intracranial pressure, such as elevation of the head of the bed to 30 degrees, mannitol, hyperventilation, and ventriculostomy, may be based on the consensus of the management team. The use of mannitol and hyperventilation are reserved for incipient brain herniation syndromes. After the patient is stabilized, catheter-based angiography may be necessary if a ruptured berry aneurysm or arteriovenous malformation is suspected.

In GUSTO-I (375), 46 (17.2%) of 268 PH/subdural hematoma patients underwent neurosurgical evacuation by open craniotomy or burr-hole craniectomy. Patients who underwent neurosurgical evacuation had significantly higher 30-day survival rates than patients who did not (65.2% versus 35.1%, p less than 0.001), particularly in patients with PH. Patients with both PH and subdural hematoma had a very poor prognosis regardless of surgical treatment. There was a trend for improved functional status in patients who underwent neurosurgical evacuation compared with those who did not (nondisabling stroke 20% versus 12%, p equals 0.15). Although not definitive, these data suggest that physicians actively consider neurosurgical interventions in selected patients. For patients with spinal epidural hematoma and significant neurological deficits occurring after fibrinolysis, early multilevel decompressive laminectomy should be performed to minimize long-term disability (376). Survivors of PH/subdural hematoma/epidural hematoma should receive supportive care measures, including physical therapy, occupational therapy, speech therapy, swallowing evaluation, aspiration precautions, deep vein thrombosis (DVT) prophylaxis (pneumatic compression device), antibiotic therapy, nutritional support, and rehabilitation, where appropriate.

The risk of 30-day mortality from ICH after coronary fibrinolysis may be predicted on the basis of prior trial experience. In GUSTO-I (322), the ICH mortality rate was 59.7%. Glasgow Coma Scale score, age, time from fibrinolysis to ICH onset, hydrocephalus, herniation, mass effect, intraventricular hemorrhage, and volume and location of ICH were significant univariable predictors, with a strong trend (p equals 0.0546) for neurosurgical evacuation. The multivariable model showed that Glasgow Coma Scale score, time from thrombolysis to ICH onset, ICH volume, and age were significant predictors of mortality (377). A nomogram has been developed to calculate the risk of dying of ICH (Figure 20) (377). Prospective studies are needed to confirm the utility of this nomogram.

1. Find Points for Each Risk Factor

Age, y		Glasgow Coma Scale GCS Score		Time from Fibrinolysis to Stroke Onset, hours			Total Hemorrhagic Volume, mm^3	
Age	Points	Score	Points	Time		Points	Volume	Points
ess than or equal to 40	0	3	20	0		100	less than or equal to 50	0
45	2	4	18	20		93	60	2
50	4	5	16	40		87	80	5
55	5	6	15	60		80	100	9
60	7	7	13	80		73	120	13
65	9	8	12	100		67	140	16
70	11	9	10	120		60	160	20
75	13	10	8	140		53	180	24
80	14	11	7	160		47	200	27
85	16	12	5	180		40	220	31
90	18	13	3	200		33	240	35
		14	2	220		27	260	38
		15	0	240		20	280	42
				260		13	300	46
				280		7		
				greater than or equal to 300		0		

2. Sum Points for All Risk Factors

Age	plus	GCS score	plus	Time to stroke	plus	Volume	equals	Point Total

3. Look Up Risk Corresponding to Point Total

Points	Risk		Points	Risk		Points	Risk	
87	1%		109	30%		128	90%	
97	5%		115	50%		132	95%	
101	10%		120	70%		142	99%	

Figure 20. Nomogram for prediction of 30-day mortality following intracranial hemorrhage in patients receiving fibrinolysis. Reproduced with permission from Sloan et al. Circulation 1998;98:1376-82 (377).

6.3.1.6.3.6. Comparison of Fibrinolytic Agents

All of the fibrinolytic agents currently available and under investigation are plasminogen activators (378). They work enzymatically, directly or indirectly, to expose the active enzymatic center of plasmin. Some comparative features of the approved fibrinolytic agents for intravenous therapy are presented in Table 15 (379-381).

Data from GUSTO-I (25) and GUSTO-III (26) suggest that accelerated alteplase and reteplase (administered as a double bolus) with intravenous heparin are effective therapies for achieving early coronary reperfusion and may provide an advantage over streptokinase; however, both are substantially more expensive and confer a slightly greater risk of ICH. Thus, the cost-benefit ratio is most favorable for alteplase or reteplase in patients who present early after onset of chest pain or symptoms and in those with a large area of injury (e.g., anterior infarction) and at low risk of ICH. In ASSENT-2, weight-adjusted TNK-tPA (tenecteplase) and alteplase were compared in 16 949 patients. Covariate-adjusted 30-day mortality was virtually identical (i.e., 6.18% for tenecteplase and 6.15% for alteplase), which met the predefined criteria for equivalence. The rates of ICH were also similar (i.e., 0.93% for tenecteplase and 0.94% for alteplase), but in patients receiving tenecteplase, there were fewer systemic mild-to-moderate bleeding complications (26.3% versus 28.95%, p equals 0.0003) and less requirement for blood transfusion (4.25% versus 5.49%, p equals 0.0002) (28).

There is considerable ongoing investigation into the effectiveness of fibrinolytic therapy with various ancillary therapies (see Section 6.3.1.6.3.8). In 2 studies that evaluated the combination of hirudin (desirudin) with alteplase and streptokinase, there was no improvement in mortality rate, and the therapeutic-to-severe bleeding window appeared to be very narrow (382,383). See Section 6.3.1.6.8.1.3 for further discussion.

A number of proposals for selection of fibrinolytic regimens after GUSTO-I have been suggested (384-387). Additional considerations include avoiding the reuse of streptokinase, preferably indefinitely because of a high prevalence of potentially neutralizing antibody titers. Alternatively, Simoons and Arnold (386) proposed considering primary PCI for those at highest risk (approximately 10% of patients), alteplase for those at moderate to high risk (40%), streptokinase for those at low to moderate risk (40%), and no lytic therapy for those at lowest risk (10%). All of these recommendations await prospective testing, and no data are available to determine the best modes for routine clinical practice.

Current use rates for fibrinolytic therapy. Because many patients have contraindications or other exclusions for fibrinolytic agents, it has been difficult to ascertain the proportion of patients with ST elevation who fail to receive fibrinolytic therapy who actually should have received such therapy (388). Critical to any such assessment of appropriateness of care, however, is whether the diagnosis of STEMI was suspected on entry into the healthcare system or whether a diagnosis made after 12 to 24 hours in the hospital or at some later point before hospital discharge. Some increase in use rates probably can be achieved, but contraindications prohibit a vast increase in the rate of use of fibrinolysis.

6.3.1.6.3.7. Net Clinical Benefit

The decision to use reperfusion therapy is based on an estimate of the patient's underlying risk without treatment, the expected benefit of the treatment, and the risk of the therapy. In general, the higher the underlying risk, the more benefit that can be gained and the fewer the number of patients who need to be treated to save 1 life.

Because decisions about reperfusion must be made rapidly in order for the intervention to be maximally effective, it is

Table 15. Comparison of Approved Fibrinolytic Agents

	Streptokinase	Alteplase	Reteplase	Tenecteplase-tPA
Dose	1.5 MU over 30-60 min	Up to 100 mg in 90 min (based on weight)*	10 U × 2 each over 2 min	30-50 mg based on weight (379)†
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
90-min patency rates, approximate %	50	75	7	75 (380)
TIMI grade 3 flow, %	32	54	60	63
Cost per dose (US $)(381)	$613	$2974	$2750	$2833 for 50 mg

MU = mega units.

*Bolus 15 mg, infusion 0.75 mg/kg times 30 minutes (maximum 50 mg), then 0.5 mg/kg not to exceed 35 mg over the next 60 minutes to an overall maximum of 100 mg.

†Thirty milligrams for weight less than 60 kg; 35 mg for 60-69 kg; 40 mg for 70-79 mg; 45 mg for 80-89 kg; 50 mg for 90 kg or more.

not possible to take the time to confirm the diagnosis of STEMI before administration of therapy. Data from the Multicenter Chest Pain Study suggest that approximately 80% of patients with chest pain and ST-segment elevation who present to the ED are having a STEMI (227).

Several prediction models for short-term (30 days) (240,242,298,389-393) and long-term (1 to 6 years) (392,393) mortality after reperfusion therapy for STEMI have been developed. These models have been derived from clinical trials (240,242,389,394), administrative data sets (298,390,392), and registries (391), and some have been validated in other clinical trials (242) or registries (391,394). Performance for some of these risk-prediction models, as defined by the area under the receiver operating characteristic curve, c-index, or standardized mortality ratio, is similar, with c-indices ranging from 0.74 to 0.80 and correlation coefficients for the standardized mortality ratios ranging from 0.89 to 0.92 (298). The TIMI risk score developed in the InTIME-II trial (242) performs well compared with data from the TIMI-9 trial and NRMI-3 (394). In NRMI-3, prognostic discriminatory capacity was similar between patients who received fibrinolytics and primary PCI (c-index equals 0.80). Substantial differences in predicted mortality rates (greater than 5%) between those patients who did or did not receive reperfusion therapy were observed if the TIMI risk score was greater than or equal to 7 (394).

The expected benefit of fibrinolytic therapy can be estimated from the clinical trials (156,282). The fibrinolytic trials showed "absolute mortality reductions of about 30 per 1000 for those presenting within 0-6 h and of about 20 per 1000 for those presenting 7 to 12 h from onset, and a statistically uncertain benefit of about 10 per 1000 for those presenting at 13 to 18 h (with more randomized evidence needed in this latter group to assess reliably the net effects of treatment)" (156). The relative benefit, however, appeared to vary by age, with a smaller relative reduction in risk for the oldest patients.

The major risk of pharmacological reperfusion therapy is life-threatening hemorrhage (105). (See Section 6.3.1.6.3.2 for further information.) A study among Medicare patients identified older age, female sex, black race, prior stroke, systolic blood pressure greater than or equal to 160 mm Hg, lower weight (less than or equal to 65 kg for women, less than or equal to 80 kg for men), excessive anticoagulation (international normalized ratio [INR] greater than or equal to 4, prothrombin time greater than or equal to 24 sec), and choice of fibrinolytic therapy (tPA associated with greater risk than streptokinase) as risk factors for intracranial bleeding (246). Patients with none or 1 of these factors had a risk of 0.69% for intracranial bleeding, whereas those with 5 or more factors had a risk of 4.1%. Simoons et al., using data primarily from trials, identified older age, lower body weight (less than 70 kg), systolic blood pressure greater than or equal to 170 mm Hg or diastolic blood pressure greater than or equal to 95 mm Hg, and the use of tPA (versus streptokinase) as risk factors (329). Using these factors, a risk score was developed that classified patients with a risk of hemorrhage from 0.26% to 2.2% (for zero to 4 risk factors). Although this score uses dichotomous cutpoints for the risk factors, it is likely that the risk is a continuous function of the factor (e.g., the higher the blood pressure or the older the patient, the higher the risk) (322). Also, the studies of risk were based on older regimens of fibrinolytic therapy and higher dosages of UFH than are used currently. There is some evidence that newer agents, with increased fibrin specificity and bolus administration, may not increase the risk of ICH, but this issue deserves continued evaluation (156). In addition, the use of ancillary therapies may influence the risk of bleeding with fibrinolytic therapy.

6.3.1.6.3.8. Combination Therapy With GP IIb/IIIa Inhibitors

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 (394a) *(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)*

Studies evaluating the use of glycoprotein IIb/IIIa inhibitors as the sole means of reperfusion (i.e., without a fibrinolytic or in conjunction with PCI) do not suggest that the isolated use of a GP IIb/IIIa inhibitor restores TIMI 3 flow in a sufficient proportion of patients to make it a viable pharmacologic strategy (395a). To improve rates of achieving TIMI 3 flow by pharmacological reperfusion therapy, GP IIb/IIIa antagonists have been combined with fibrinolytic agents to achieve both platelet disaggregation and fibrinolysis (395). The phase 2 angiographic studies, TIMI-14, SPEED (Strategies for Patency Enhancement in the Emergency Department), and Intro AMI (Integrilin and low-Dose Thrombolysis in Acute Myocardial Infarction) (369,396,397), have demonstrated higher TIMI 3 flow rates at 60 to 90 minutes. When combination therapy is used, the

dose of fibrinolytic agent is reduced by 50%. A large-scale mortality study, GUSTO-V (30), tested half-dose reteplase (5 U and 5 U) and full-dose abciximab (abciximab 0.25 mg/kg bolus and 0.125 mcg/kg/min [maximum of 10 mcg/min] for 12 hours) compared with full-dose reteplase (10 U and 10 U) in 16 588 patients in the first 6 hours of STEMI. Thirty-day mortality rates were similar in the 2 groups (5.9% versus 5.6%). However, nonfatal reinfarction rates were reduced in the combination therapy group (2.3% versus 3.5%, p less than 0.0001), as were other complications of MI, including VF and tachycardia, high-grade AV block, and septal or free-wall rupture. ICH rates were the same (0.6%), but moderate to severe bleeding was significantly increased from 2.3% to 4.6% (p less than 0.001). Excess bleeding risks appear to be limited to those over the age of 75 years, and the greatest mortality benefit was seen for those with anterior MI. ICH rates for those older than 75 years were 2.1% versus 1.1% (p equals 0.069) for combination versus full-dose reteplase. In contrast, the rates were similar for those younger than 75 years (0.5% versus 0.4%). However, there was an interaction between age and risk of ICH with therapy. Younger patients (age less than 70 years) appeared to have significantly lower ICH rates with combination therapy (398). Despite the reduction in reinfarction by combination therapy, the 1-year mortality rates were the same (8.38%) in both groups (399). Although early reinfarction was associated with a marked increase in 1-year mortality, (22.6% versus 8.0% without reinfarction), this did not result in an overall mortality difference owing to the low reinfarction rates. For those younger than 75 years with anterior MI, 30-day mortality was 4.4% for combination therapy versus 5.8% (p equals 0.029) for full-dose rPA, and 1-year mortality was 7.1% versus 8.0% (p equals 0.260), respectively.

ASSENT-3 (31) randomized 6095 patients with STEMI to full-dose tenecteplase with UFH versus full-dose tenecteplase with enoxaparin or half-dose tenecteplase plus abciximab plus weight-adjusted, reduced-dose UFH. Similar to the GUSTO-V trial, combination of abciximab (abciximab 0.25 mg/kg bolus and 0.125 mcg/kg/min [maximum of 10 mcg/min] for 12 hours) and half-dose tenecteplase did not reduce mortality compared with full-dose tenecteplase but did result in significantly reduced in-hospital infarction and refractory ischemia. Notably, the major bleeding rate other than ICH, which was the same in the 2 groups, was increased from 2.2% to 4.3% (p less than 0.0005). Those over the age of 75 years were at greatest risk for excess bleeding, with a 3-fold increase in major bleeding complications. The tenecteplase plus enoxaparin arm showed superiority compared with UFH (see Section 6.3.1.7.8.2.1). The need for urgent PCI was reduced in the GP IIb/IIIa antagonist and fibrinolytic combination therapy arms in both trials. The heparin regimen, when combination therapy is used, is a weight-adjusted bolus of 40 U/kg (ASSENT-3) or 60 U/kg (GUSTO-V) followed by a reduced infusion dose of 7 U/kg/h. The lower bolus dose is preferable for patients who have an increased risk for bleeding.

Given the observation that patients with TIMI 3 flow before primary PCI have the best outcomes (346) and given the role of GP IIb/IIIa antagonists in PCI, some have hypothesized that administration of combination GP IIb/IIIa antagonists and half-dose fibrinolytics will facilitate primary PCI, particularly when it cannot be accomplished very rapidly. This remains to be tested prospectively in appropriately sized trials. Combination pharmacological reperfusion regimens may be associated with a slightly higher frequency of ICH and a slightly lower frequency of cerebral infarction and stroke of unknown cause than other reperfusion regimens (Table 14) (26-30,31,33,158,261,320,322,324,331,351-369,400).

6.3.1.6.4. PERCUTANEOUS CORONARY INTERVENTION. Percutaneous coronary intervention is a very effective method for re-establishing coronary perfusion and is suitable for at least 90% of patients. Considerable data (40,282,401) support the use of PCI for patients with STEMI. Reported rates of achieving TIMI 3 flow range from 70% to 90%. There is a 15% reocclusion rate after PTCA and a 5% reocclusion rate after stenting (402). Although most evaluations of PCI have been in patients who are eligible to receive fibrinolytic therapy, considerable experience supports the value of PCI for patients who may not be suitable for fibrinolytic therapy because of an increased risk of bleeding (403).

6.3.1.6.4.1. 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 (VSR) or severe 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)***

Acute cardiac catheterization has been proposed as an anatomic risk stratification strategy. A subset of patients will have severe 3-vessel or left main disease or anatomic features unfavorable for PCI and may be candidates for urgent or emergency CABG. Another subset of patients will have spontaneously reperfused and will have minimal evidence of atherosclerotic obstruction. They can be treated medically, which avoids the risks of fibrinolytic therapy or PCI. Additionally, identification of high-risk patients may facilitate additional strategies that will improve outcome, whereas low-risk patients may be eligible for early hospital discharge. Coronary angiography should not be performed in patients

with extensive comorbidities or who will not consent to coronary revascularization regardless of the findings.

6.3.1.6.4.2. Primary PCI

See Table 11 for additional consideration for selecting reperfusion therapy.

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 (a laboratory that 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. **Primary PCI should be performed as quickly as possible with a goal of a medical contact–to-balloon or door-to-balloon interval of within 90 minutes. *(Level of Evidence: B)***
   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 interval as short as possible and a goal of within 90 minutes. *(Level of Evidence: B)***
   d. **Primary PCI should be performed 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)***
   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 minutes). *(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 has been compared with fibrinolytic therapy in 22 randomized clinical trials (173,177,306,307,404-421). An additional trial, SHOCK (301), which compared medical stabilization with immediate revascularization for cardiogenic shock, was included along with the above 22 trials in an overview of primary PCI versus fibrinolysis (40). These investigations demonstrate that PCI-treated patients experience lower short-term mortality rates (5.0% versus 7.0%, RR 0.70, 95% CI 0.58 to 0.85, p equals 0.0002), less nonfatal reinfarction (3.0% versus 7.0%, RR 0.35, 95% CI 0.27 to 0.45, p equals 0.0003), and less hemorrhagic stroke (0.05% versus 1.0%, RR 0.05, 95% CI 0.006 to 0.35, p equals 0.0001) than those treated by fibrinolysis but with an increased risk for major bleeding (7.0% versus 5.0%, RR 1.3, CI 1.02 to 1.65, p equals 0.032) (40). These results were achieved in medical centers with experienced providers and under circumstances in which PCI could be performed promptly after patient presentation (Figure 14) (40).

Additional considerations that affect the magnitude of the difference between PCI- and fibrinolysis-treated patients include the fact that UFH was used as the antithrombin with fibrinolytics as opposed to other antithrombins such as enoxaparin (see Section 6.3.1.6.8.1.1) or bivalirudin (see Section 6.3.1.6.8.1.2) that are associated with a reduction in the rate of recurrent MI after fibrinolysis; a smaller but statistically significant advantage for PCI compared with a fib-

rin-specific fibrinolytic versus streptokinase; and variation among the PCI arms as to whether a stent was implanted or GP IIb/IIIa antagonists were administered. Figure 14 shows the short-term and long-term outcomes of patients with STEMI treated by fibrinolysis versus PCI and the number of patients who need to be treated to prevent 1 event or cause 1 harmful complication when selecting PCI instead of fibrinolysis as the reperfusion strategy (Figure 14) (40). When primary PCI is compared with tPA and the SHOCK trial is excluded, the mortality rate is 5.5% versus 6.7% (OR 0.81%, 95% CI 0.64 to 1.03, p equals 0.081) (421a).

There is serious and legitimate concern that a routine policy of primary PCI for patients with STEMI will result in unacceptable delays in achieving reperfusion in a substantial number of cases and produce less than optimal outcomes if performed by less-experienced operators. The mean time delay for PCI instead of fibrinolysis in the randomized studies was approximately 40 minutes (40). Strict performance criteria must be mandated for primary PCI programs so that long door-to-balloon times and performance by low-volume or poor-outcome operators/laboratories do not occur. Interventional cardiologists and centers should strive for outcomes to include 1) medical contact–to-balloon or door-to-balloon times less than 90 minutes, 2) TIMI 2/3 flow rates obtained in more than 90% of patients, 3) emergency CABG rate less than 2% among all patients undergoing the procedure, 4) actual performance of PCI in a high percentage of patients (85%) brought to the laboratory, and 5) risk-adjusted in-hospital mortality rate less than 7% in patients without cardiogenic shock. This would result in a risk-adjusted mortality rate with PCI comparable to that reported for fibrinolytic therapy in fibrinolytic-eligible patients (40) and would be consistent with previously reported registry experience (422-425). Otherwise, the focus of treatment should be the early use of fibrinolytic therapy (Figure 14) (40).

PCI appears to have its greatest mortality benefit in high-risk patients. In patients with cardiogenic shock, an absolute 9% reduction in 30-day mortality with coronary revascularization instead of immediate medical stabilization was reported in the SHOCK trial (301). In NRMI-II, patients with CHF had a 33% relative risk reduction with primary PCI compared with a 9% relative risk reduction with fibrinolytic therapy (302). Primary PCI in patients with anterior STEMI reduces mortality compared with fibrinolytic therapy, but there is no difference in patients with nonanterior STEMI (426,427).

Time from symptom onset to reperfusion is an important predictor of patient outcome. Two studies (294,295) have reported increasing mortality rates with increasing door-to-balloon times. Other studies have shown smaller infarct size, better LV function, and fewer complications when reperfusion occurs before PCI (345,346,428). An analysis of the randomized controlled trials that compared fibrinolysis with a fibrin-specific agent versus primary PCI suggests that the mortality benefit with PCI exists when treatment is delayed by no more than 60 minutes (Figure 15) (305). Mortality increases significantly with each 15-minute delay in the time between arrival and restoration of TIMI 3 flow (door-to–TIMI 3 flow time), further underscoring the importance of timely reperfusion in patients who undergo primary PCI (429). Importantly, after adjustment for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with 1-year mortality in patients undergoing primary PCI for STEMI (RR equals 1.08 for each 30-minute delay from symptom onset to balloon inflation, p equals 0.04) (Figure 21) (275). Given that the door-to-needle time goal is 30 minutes, this Writing Committee joins the Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology in lowering the recommended medical contact–to-balloon or door-to-balloon time goal from 120 to 90 minutes in an attempt to maximize the benefits for reperfusion by PCI (297) (Figure 22) (294).

If the expected door-to-balloon time exceeds the expected door-to-needle time by more than 60 minutes, fibrinolytic treatment with a fibrin-specific agent should be considered unless it is contraindicated. This is particularly important when symptom duration is less than 3 hours but is less important with longer symptom duration, when less ischemic myocardium can be salvaged. In both the CAPTIM trial (173), which showed lower mortality with prehospital fibrinolysis than with primary PCI, and the PRAGUE-2 trial (177), which showed lower mortality with primary PCI after interhospital transfer than with on-site fibrinolysis, PCI was superior to fibrinolysis when symptom duration was greater than 2 to 3 hours but not when symptom duration was shorter (see Section 6.3.1.6.2.1). In the early hours of STEMI, prompt fibrinolytic therapy can decrease infarct size and the risk of developing cardiogenic shock (176).

6.3.1.6.4.2.1. Complications of primary PCI.

Potential complications of an invasive strategy for treating STEMI include problems with the arterial access site; adverse reactions to volume loading, contrast medium, and antithrombotic medications; technical complications; and reperfusion events. Reocclusion occurs in 10% to 15% of patients after PTCA but in fewer than 5% after stent implantation. Likewise, angiographic restenosis occurs in 30% to 40% of patients after PTCA but in 15% to 20% after stent implantation. The management of these complications is beyond the scope of this guideline (430-432).

6.3.1.6.4.2.2. 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:

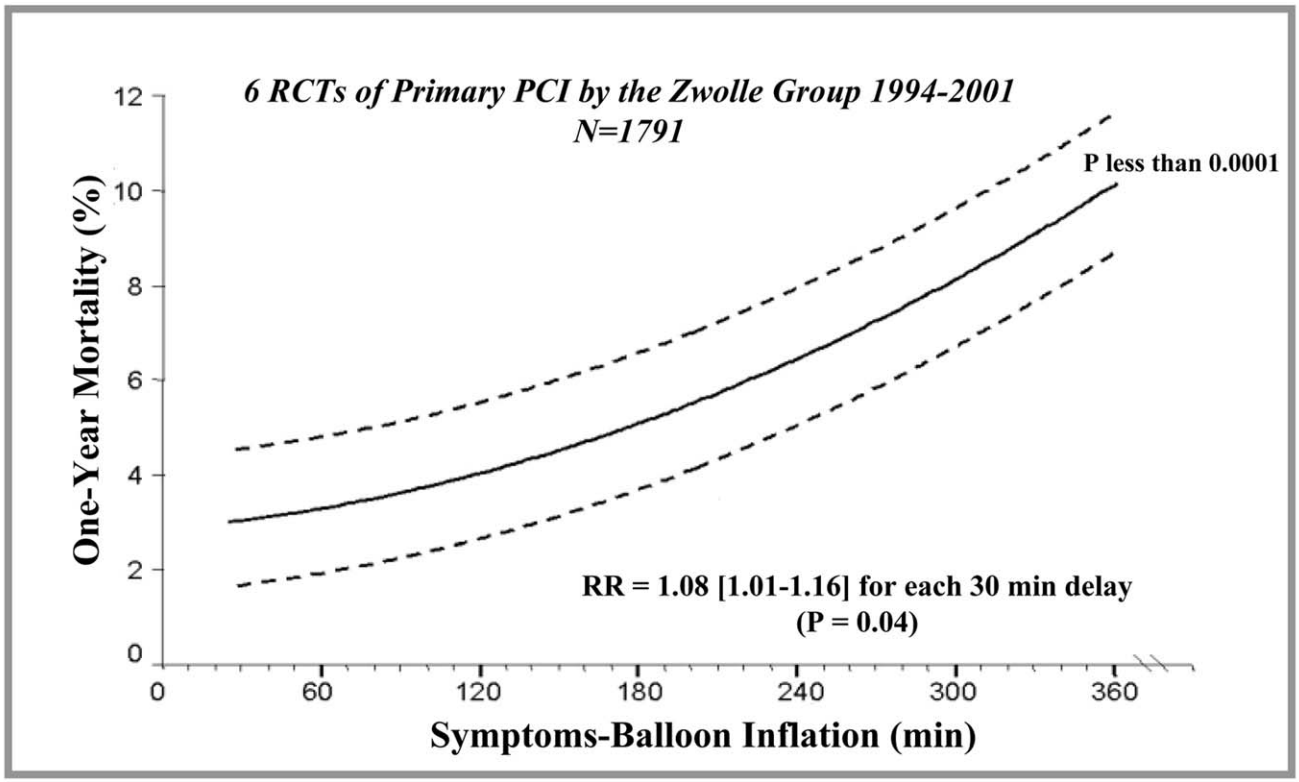


Figure 21. Symptom onset-balloon time and mortality in primary PCI for ST-elevation myocardial infarction. RCT = randomized controlled trial; PCI = percutaneous coronary intervention. The relationship between time-to-treatment and 1-year mortality, as continuous functions, was assessed using a quadratic regression model. The dotted lines represent 95% confidence intervals of the predicted mortality. Modified with permission from De Luca. Circulation 2004;109:1223-25 (275).

a. **Severe CHF** ***(Level of Evidence: C)***
b. **Hemodynamic or electrical instability** ***(Level of Evidence: C)***
c. **Persistent ischemic symptoms.** ***(Level of Evidence: C)***

Randomized controlled trials evaluating the outcome of PCI for patients who present with STEMI but who are ineligible for fibrinolytic therapy have not been performed. Few data are available to characterize the value of primary PCI for this subset of patients with STEMI; however, the recommendations in Section 4.2 are applicable to these patients. Nevertheless, these patients are at increased risk for mortality (433), and there is a general consensus that PCI is an appropriate means for achieving reperfusion in those who cannot receive fibrinolytics because of increased risk of bleeding (403,434-436).

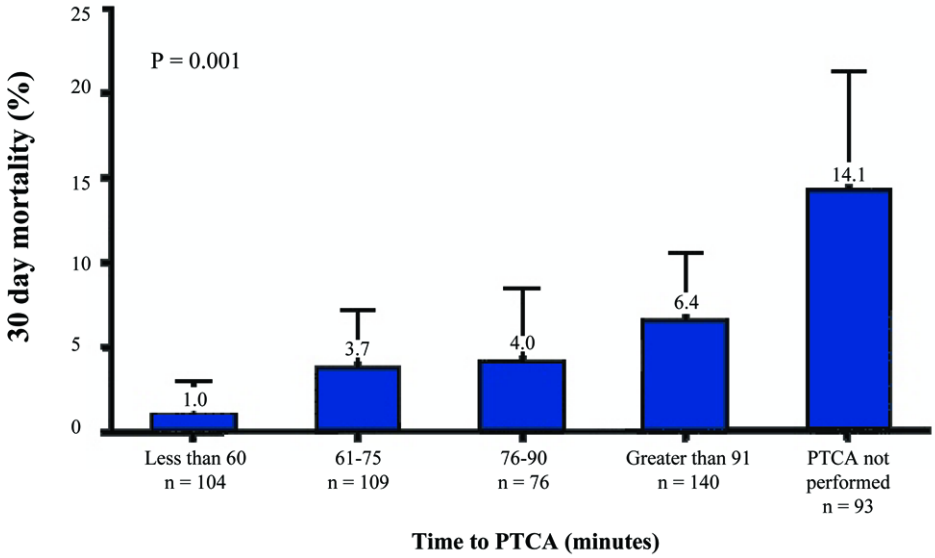


Figure 22. Relationship between 30-day mortality and time from study enrollment to first balloon inflation. Patients assigned to angioplasty in whom angioplasty was not performed are also shown. PTCA = percutaneous transluminal coronary angioplasty. Reprinted with permission from Berger et al. Circulation 1999;100:14-20 (294).

6.3.1.6.4.2.3. Primary PCI without on-site cardiac surgery.

Class IIb

Primary PCI might be considered in hospitals without on-site cardiac surgery, provided that a proven plan for rapid transport to a cardiac surgery operating room exists 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 performing 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 capabilities 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)*

Reports on emergency primary PCI from hospitals without established open heart surgery or elective PCI programs have demonstrated generally favorable results (307,437-450). PCI in the early phase of an acute STEMI can be difficult and requires even more skill and experience than routine PCI in the stable patient. The need for an experienced operator and experienced laboratory technical support with availability of the broad range of catheters, guidewires, stents, and other devices (e.g., intra-aortic balloon pump [IABP]) required for optimum results in an acutely ill patient is of major importance. Careful patient selection and continuous quality improvement are critical components of a successful program. If these complex patients are treated by interventionalists with limited experience at hospitals with low volume, then the gains of early intervention may be lost because of increased complications. In such circumstances, transfer to a center that routinely performs complex PCI will often be a more effective and efficient course of action. Fibrinolysis is an acceptable form of therapy and is preferable to primary PCI by an inexperienced team.

Criteria have been suggested for the performance of primary PCI at hospitals without on-site cardiac surgery (432,445) (Tables 16 and 17). Large-scale registries have shown an inverse relationship between the number of primary PCI procedures performed and in-hospital mortality (295,303,304). The data suggest that both door-to-balloon time and in-hospital mortality are significantly lower in institutions that perform a minimum of 36 primary PCI procedures per year (295). Suboptimal results may relate to operator/staff inexperience and capabilities and to delays in performing PCI for logistical reasons. From clinical data and expert consensus, the Committee recommends that primary PCI for acute STEMI performed at hospitals without established elective PCI programs should be restricted to those institutions capable of performing a requisite minimum number of primary PCI procedures (36 per year) with a proven plan for rapid and effective PCI and rapid access to cardiac surgery in a nearby hospital. The benefit of primary PCI is not well established for operators who perform fewer than 75 PCIs per year or in a hospital that performs fewer than 36 primary PCI procedures per year. In addition, the benefit of timely reperfusion of the infarct artery by primary PCI at sites without on-site surgery must be weighed against the small but finite risk of harm to the patient related to the time required to transfer the patient to a site with CABG surgery capabilities (452,453).

Table 16. Criteria for Performance of Primary PCI at Hospitals Without Onsite Cardiac Surgery

The operators must be experienced interventionalists who regularly perform elective PCI at a surgical center (at least 75 cases/year). The catheterization laboratory must perform a minimum of 36 primary PCI procedures per year.
The nursing and technical catheterization laboratory staff must be experienced in handling acutely ill patients and must be comfortable with interventional equipment. They must have acquired experience in dedicated interventional laboratories at a surgical center. They participate in a 24-hour, 365-day call schedule.
The catheterization laboratory itself must be well equipped, with optimal imaging systems, resuscitative equipment, and IABP support, and must be well stocked with a broad array of interventional equipment.
The cardiac care unit nurses must be adept in hemodynamic monitoring and IABP management.
The hospital administration must fully support the program and enable the fulfillment of the above institutional requirements.
There must be formalized written protocols in place for immediate and efficient transfer of patients to the nearest cardiac surgical facility that are reviewed/tested on a regular (quarterly) basis.
Primary PCI must be performed routinely as the treatment of choice around the clock for a large proportion of patients with STEMI, to ensure streamlined care paths and increased case volumes.
Case selection for the performance of primary PCI must be rigorous. Criteria for the types of lesions appropriate for primary PCI and for the selection for transfer for emergent aortocoronary bypass surgery are shown in Table 17.
There must be an ongoing program of outcomes analysis and formalized periodic case review.
Institutions should participate in a 3- to 6-month-period of implementation, during which time development of a formalized primary PCI program is instituted that includes establishment of standards, training of staff, detailed logistic development, and creation of a quality assessment and error management system.

PCI = percutaneous coronary intervention; IABP = intra-aortic balloon pump; STEMI = ST-elevation myocardial infarction.
Modified from Wharton et al. J Am Coll Cardiol 1999;33:1257-65 (445).

Table 17. Patient Selection for Primary PCI and Emergency Aorto-Coronary Bypass at Hospitals Without Onsite Cardiac Surgery (445)

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 (432)
Infarct-related lesions of small or secondary vessels
Hemodynamically significant lesions in other than the infarct artery
Transfer for emergency aortocoronary bypass surgery patients:
After primary PCI of occluded vessels if high-grade residual left main or multivessel coronary disease with clinical or hemodynamic instability present
Preferably with IABP support

PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction; IABP = intra-aortic balloon pump.

6.3.1.6.4.2.4. Interhospital transfer for primary PCI.

The enthusiasm for primary PCI has led to the concept of emergency interhospital transfer for catheter-based reperfusion rather than fibrinolytic therapy in the initial hospital (454-456). Complication rates are low during transport, but time to reperfusion is delayed, which results in larger infarct size and lower LVEF (457). However, as noted in Section 6.3.1.6.2.1, selection bias of patients enrolled in randomized trials likely resulted in an underestimation of the risk of interhospital transfer expected in routine practice. Five randomized trials enrolled 2466 patients, with favorable results for PCI versus fibrinolytic therapy (177,306,408,419,421). Mortality was reduced with PCI (6.8% versus 9.6%, RR 0.69, 95% CI 0.51 to 0.0.92, p equals 0.01), as was the combined end point of death, nonfatal reinfarction, and stroke (8.5% versus 15.5%, RR 0.51, 95% CI 0.39 to 0.65, p less than 0.0001). Importantly, mean time to treatment was delayed only 44 minutes in these studies (Figure 23) (177,306). In contrast, the time from presentation at the door of the first hospital to balloon inflation in the second hospital, as recorded in 1346 patients in NRMI-4, was 185 minutes in the United States in 2002 (Figure 24) (458). Emergency transport in Europe is centrally organized and more efficient than in the United States (Table 18) (177,306,408,419,421,459) (Van de Werf; oral presentation, American College of Cardiology 52nd Annual Scientific Session, Chicago, IL, March 2003). Delays in door-to-balloon time versus door-to-needle time of more than 60 minutes because of interhospital transfer might negate the potential mortality benefit of transfer for primary PCI over imme-

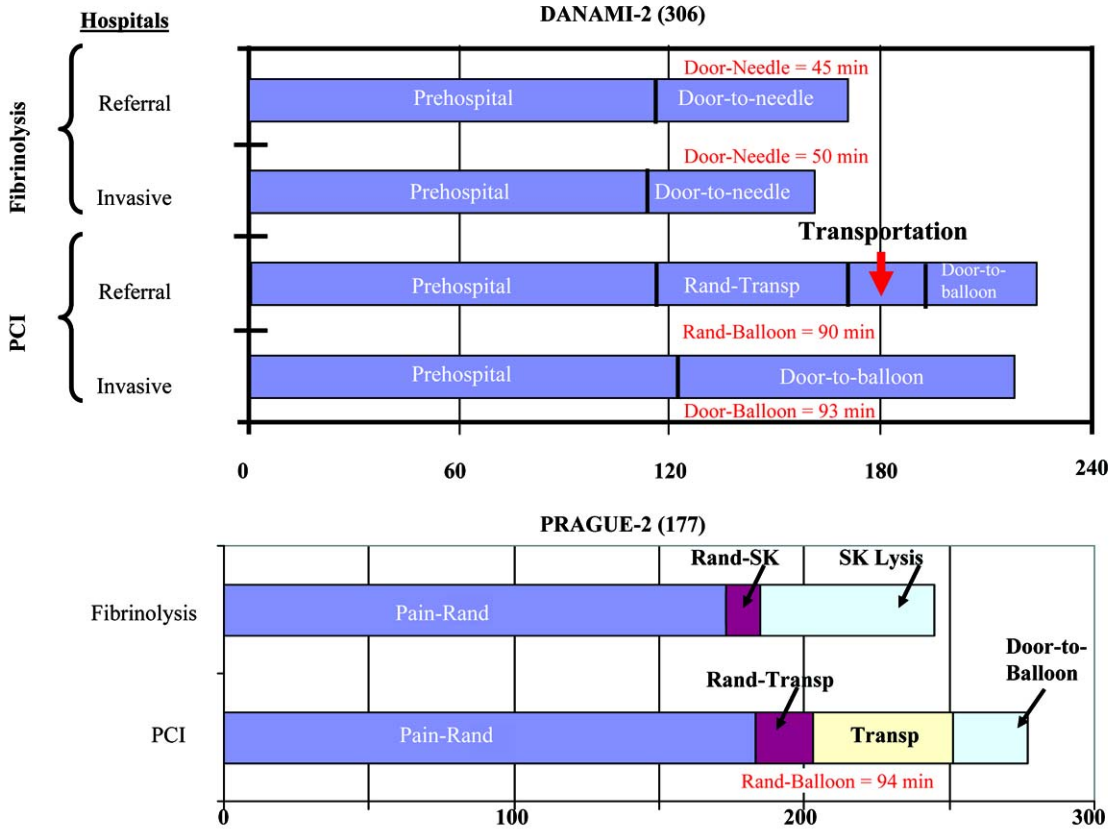


Figure 23. Comparison of elapsed time to fibrinolysis versus primary PCI. Time is presented as a continuous variable in minutes on the horizontal axis. For DANAMI-2, times reflect components of delay from symptom onset to randomization (vertical bar) and are further separated according to whether patients presented at community referral hospitals versus those equipped for primary PCI. For those patients randomized to PCI at a referral hospital, the 3 components of delay after randomization are related to duration of stay at referral hospital, time for transport to PCI hospital and delay from arrival at PCI hospital to balloon inflation. PCI = percutaneous coronary intervention; Rand = Randomization; SK = streptokinase; Transp = Transportation. PRAGUE-2 data modified from Widimsky et al. Eur Heart J 2003; 24:94-104.

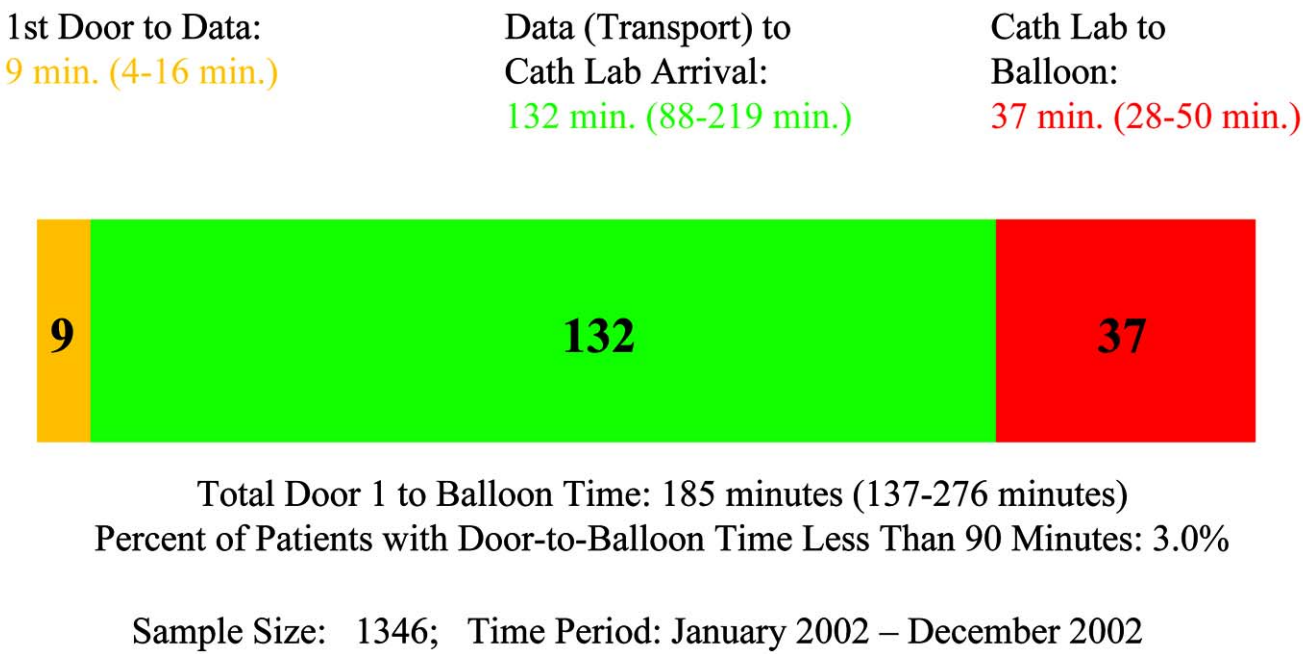


Figure 24. Door-to-balloon times: patients transferred in NRMI 4. Data are expressed in minutes as median time (25th percentile-75th percentile) Cath Lab = catheterization laboratory. Modified from NRMI-4 Investigators: The National Registry of Myocardial Infarction-4 Quarterly Report. Genentech, South San Francisco, CA; March, 2003:2 (458).

diate intravenous fibrinolysis with a fibrin-specific agent as shown in these trials (305). To achieve optimal results, time from the first hospital door to the balloon inflation in the second hospital should be as short as possible, with a goal of within 90 minutes. Significant reductions in door-to-balloon times might be achieved by directly transporting patients to PCI centers rather than transporting them to the nearest hospital, if interhospital transfer will subsequently be required to obtain primary PCI.

6.3.1.6.4.3. Primary Stenting

Of the 22 randomized trials that compared primary PCI with fibrinolytic therapy, 12 involved a comparison of primary PCI with stenting and fibrinolytic therapy (40,173,177,306,307,408,409,414,417-421). These investigations demonstrate that PCI-treated patients experience lower mortality rates (5.9% versus 7.7%, OR 0.75, 95% CI 0.60 to 0.94, p equals 0.013), less reinfarction (1.6% versus 5.1%, OR 0.31, 95% CI 0.21 to 0.44, p equals 0.0001), and less hemorrhagic stroke than those treated by fibrinolysis (40). Compared with PTCA, intracoronary stents achieve a better immediate angiographic result with a larger arterial lumen, less reocclusion and restenosis of the infarct-related artery, and fewer subsequent ischemic events.

Primary stenting has been compared with primary angioplasty in 9 studies (38,37,460-467). There were no differences in mortality (3.0% versus 2.8%) or reinfarction (1.8% versus 2.1%) rates. However, major adverse cardiac events were reduced, driven by the reduction in subsequent target-vessel revascularization with stenting (Figure 25) (37).

Preliminary reports suggest that compared with conventional bare metal stents, drug-eluting stents are not associated with increased risk when used for primary PCI in patients with STEMI (468). Postprocedure vessel patency, biomarker release, and the incidence of short-term adverse events were similar in patients receiving sirolimus (n equals 186) or bare metal (n equals 183) stents. Thirty-day event rates of death, reinfarction, or revascularization were 7.5% versus 10.4%, respectively (p equals 0.4) (468).

Table 18. Transport of Patients With STEMI for Primary PCI

Study (Reference)	No. Transported	Distance, km	Time Between Randomization and First Balloon Inflation, min
Vermeer et al. (419)	75	25-50	85*
PRAGUE-1 (408)	101	5-74	80*
AIR-PAMI (421)	71	51 plus or minus 58*	155†
PRAGUE-2 (177)	429	5-120	97*
DANAMI-2 (306)	559	3-150	90†
Total	1235	3-150	

*Mean.
†Median.

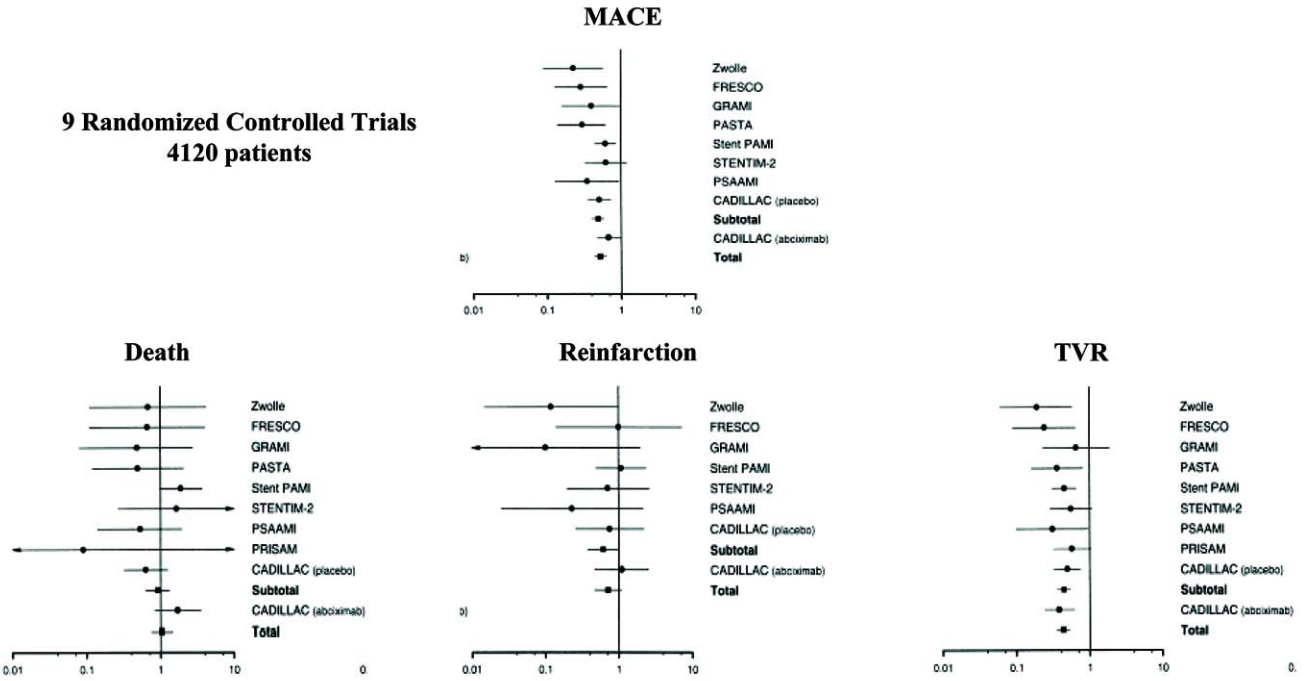


Figure 25. Primary stenting versus primary angioplasty. Odds Ratios and their 95% confidence intervals for primary stenting versus primary angioplasty for the risk of death, reinfarction, target vessel revascularization (TVR), and major adverse cardiac events (MACE) over a 6- to 12-month follow-up after ST-elevation myocardial infarction (STEMI). The meta-analysis was performed without (subtotal) and with (total) the abciximab arms of the CADILLAC trial. Modified from Zhu M et al. Am J Cardiol 2001;88:299. Copyright 2001, with permission from Excerpta Medica, Inc. (37).

6.3.1.6.4.4. Facilitated PCI

Class IIb

Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low. *(Level of Evidence: B)*

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacological regimen such as full-dose fibrinolysis, half-dose fibrinolysis, a GP IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolytic therapy and a platelet GP IIb/IIIa inhibitor. Facilitated PCI should be differentiated from primary PCI without fibrinolysis or GP IIb/IIIa inhibitor therapy, from primary PCI with a GP IIb/IIIa inhibitor started at the time of PCI, and from rescue PCI after unsuccessful fibrinolysis. Potential advantages include earlier time to reperfusion, improved patient stability, greater procedural success rates, higher TIMI flow rates, and improved survival rates (36,346,428,469,470). However, preliminary studies have not demonstrated any benefit in reducing infarct size or improving outcomes (471-473). It is unlikely that this strategy would be beneficial in low-risk patients.

A strategy of facilitated PCI holds promise in higher-risk patients when PCI is not immediately available. Potential risks include increased bleeding complications, especially in those 75 years of age or older (see Section 6.3.1.6.3.8), and potential limitations include added cost. Several randomized trials of facilitated PCI with a variety of pharmacological regimens are in progress (473a).

6.3.1.6.4.5. Rescue PCI

Class I

1. **Rescue PCI should be performed in 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: B)***
2. **Rescue PCI should be performed in patients with severe CHF and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. *(Level of Evidence: B)***

Class IIa

1. **Rescue 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 who 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 who agree to invasive care may be selected for such an invasive strategy. *(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)***

Immediately after failed fibrinolysis. Intravenous fibrinolytic therapy successfully restores coronary TIMI 2/3 flow at 90 minutes in 50% to 85% of patients with STEMI (474). In those in whom fibrinolysis is unsuccessful, antegrade coronary flow can usually be restored with PCI. Several studies have demonstrated the marked beneficial effect of infarct-related artery patency (obtained via endogenous, pharmacological, or mechanical recanalization) on survival in patients with STEMI (475,476). Survivors of STEMI with a patent infarct-related artery demonstrated at 90 minutes after treatment have an improved long-term outcome compared with those with an occluded infarct-related artery, even when LV systolic function is similar (476). Rescue (also known as salvage) PCI is defined as PCI within 12 hours after failed fibrinolysis for patients with continuing or recurrent myocardial ischemia. Rescue PCI has resulted in higher rates of early infarct artery patency, improved regional infarct-zone wall motion, and greater freedom from adverse in-hospital events than with a deferred PCI strategy or medical therapy. The Randomized Evaluation of Rescue PCI with Combined Utilization End Points (RESCUE) trial demonstrated a reduction in rates of in-hospital death and a combined end point of death and CHF that was maintained up to 1 year after study entry for patients presenting with anterior STEMI who failed fibrinolytic therapy, when PCI was performed within 8 hours after the onset of symptoms (477). Improvement in TIMI grade flow from less than or equal to 2 to 3 may offer additional clinical benefit. Similar data are not available for patients with nonanterior STEMI.

A major problem in adopting a strategy of rescue PCI lies in the limitation of accurate identification of patients for whom fibrinolytic therapy has not restored antegrade coronary flow. Unless unsuccessful fibrinolysis is recognized and corrected quickly (within 3 to 6 hours of onset of symptoms), salvage of ischemic myocardium is unlikely. Unfortunately, clinical markers of reperfusion, such as relief of ischemic-type chest discomfort, partial resolution of ST-segment elevation, and reperfusion arrhythmias, have limited predictive value in identifying failure of fibrinolysis (478). In a prior era in which the practice of PCI was less mature, immediate catheterization of all patients after fibrinolytic therapy to identify those with an occluded infarct artery was found to be impractical, costly, and often associated with bleeding complications (479,480). This strategy is being re-evaluated in clinical trials testing facilitated PCI in the contemporary PCI setting.

Even in the patient with documented failure of fibrinolysis, rescue PCI has limitations. Because extensive myocardial necrosis occurs when coronary occlusion has been present for more than 3 hours (18), PCI may not salvage a substantial amount of myocardium, considering the time delay associated with presentation of the patient to the hospital after onset of symptoms, infusion of the fibrinolytic agent, recognition of failed fibrinolysis, and subsequent initiation of PCI. Rescue PCI fails to reestablish antegrade coronary flow in approximately 10% of patients, and reocclusion of the infarct artery occurs in as many as 20% of the remainder (481), although use of GP IIb/IIIa inhibitors and stent implantation may improve these results. Unsuccessful rescue PCI is associated with a high mortality rate (482,483). Finally, coronary reperfusion occurs over the subsequent hours after fibrinolytic therapy in many patients. Although infarct artery patency is achieved in only 50% to 85% of patients 90 minutes after fibrinolytic therapy, it rises to 90% by 24 hours (474). Such late reperfusion may improve survival without the risk of invasive procedures coupled with fibrinolytic therapy. Confounding the issue, both fibrinolytic therapy and PCI may successfully restore flow in the epicardial artery but fail to improve microvascular perfusion.

Hours to days after failed fibrinolysis. Patency of the infarct-related artery is an important predictor of mortality in survivors of STEMI (475,476). Compared with those with a patent infarct artery, survivors of STEMI with a persistently occluded artery after fibrinolysis, PCI, or no reperfusion therapy have 1) increased LV dilatation (484), 2) a greater incidence of spontaneous and inducible ventricular arrhythmias (485), and 3) a poorer prognosis (486). On the basis of observational and experimental data, it has been hypothesized that infarct artery patency may favorably influence LV remodeling and electrical stability, even if accomplished at a time when salvage of ischemic myocardium is unlikely (i.e., more than 12 hours to days after coronary artery occlusion). Five small randomized trials, which enrolled a total of 562 patients, have directly tested the hypothesis that mechanical opening of persistent total occlusions late after MI will improve long-term LV remodeling and clinical outcomes (the late open-artery hypothesis). Most studies enrolled a combination of patients that included those who had failed fibrinolysis and those who had not received reperfusion therapy (487-489), with a range from almost no fibrinolytic therapy (490) to fibrinolytic therapy in nearly all patients (491). There was wide variation in the effect of routine PCI compared with only medical therapy on LV size and function. Most studies showed no significant differences between the treatment groups (487,488). One single-center study of 83 patients with occlusions of the left anterior descending coronary artery (LAD) reported improved LV volumes and clinical outcomes (composite of CHF, MI, and death) at 6 months in the PCI group (490). In contrast, a multicenter study of 66 patients with LAD occlusions reported significantly worse LV remodeling, with progressive LV dilation at 1 year and more clinical events in the PCI group than in those assigned to optimal medical therapy alone (491). The latter included very high rates of beta-blocker and ACE inhibitor use. The largest multicenter study, DECOPI, enrolled 212 patients and reported no difference in the primary end point, the composite of death, VT, and MI at 6 months (Steg PG; oral presentation, European Society of Cardiology Congress 2003, Vienna, Austria, September 2003). Stents were used in 80% of patients in the PCI group, and GP IIb/IIIa antagonists were

used in 9%. The study reached fewer than one third of the target sample size and was severely underpowered, as were all the other studies, to assess clinical events.

There are no convincing data to support the routine use of adjuvant PCI days after failed fibrinolysis or for patients who do not receive reperfusion therapy. Nevertheless, this is being done in some patients with STEMI as an extension of the invasive strategy for patients with NSTEMI. The Occluded Artery Trial (OAT) is currently randomizing patients to test whether routine PCI days to weeks after MI improves long-term clinical outcomes in asymptomatic high-risk patients with an occluded infarct-related artery (493).

6.3.1.6.4.6. PCI for Cardiogenic Shock

Class I

Primary PCI 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)*

Class IIa

Primary PCI 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 are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. *(Level of Evidence: B)*

Observational studies support the value of PCI for patients who develop cardiogenic shock in the early hours of STEMI. For patients who do not have mechanical causes of shock, such as acute MR or septal or free wall rupture, mortality among those having PCI is lower than for those treated medically. However, undergoing cardiac catheterization alone, with or without PCI, is associated with a lower mortality owing to patient selection bias (494).

Two small randomized clinical trials (301,495) have further clarified the role of emergency revascularization in STEMI complicated by cardiogenic shock. Both showed a statistically insignificant but clinically important absolute 9% reduction in 30-day mortality. In the SHOCK trial (301), the survival curves continued to progressively diverge such that at 6 months and 1 year, there was a significant mortality reduction with emergency revascularization (53% versus 66%, p less than 0.03) (184). The prespecified subgroup analysis of patients less than 75 years old showed an absolute 15% reduction in 30-day mortality (p less than 0.02), whereas there was no apparent benefit for the small cohort (n equals 56) of patients more than 75 years old. These data strongly support the approach that patients younger than 75 years with STEMI complicated by cardiogenic shock should undergo emergency revascularization and support measures. Three registries (496-498) have demonstrated a marked survival benefit for elderly patients who are clinically selected for revascularization (approximately 1 of 5 patients), so age alone should not disqualify a patient for early revascularization. (See Section 7.6.5.)

Several additional discussions elsewhere in this guideline are important to consider in these patients. Intra-aortic balloon pump support or ventricular assist devices can stabilize hemodynamics so that revascularization procedures can be performed (see Section 7.6.7.6). Post hoc analyses (499-501) have suggested that GP IIb/IIIa inhibitors reduce mortality, but the studies are limited by lower than expected mortality rates, larger than expected mortality reduction, and small sample sizes (see Section 6.3.1.6.8.2.3). Although PCI in a noninfarct artery is not recommended in stable patients, it can be beneficial in hemodynamically compromised patients if the stenotic artery perfuses a large area of myocardium and the procedure can be done efficiently. In patients with significant left main disease or severe 3-vessel disease and without RV infarction or major comorbidities such as renal insufficiency or severe pulmonary disease, CABG can be considered as the revascularization strategy (see Section 6.3.1.6.5) (Figure 26) (502).

6.3.1.6.4.7. Percutaneous Coronary Intervention After Fibrinolysis

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

Class IIa

1. **It is reasonable to perform routine PCI in patients with 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

Routine PCI might be considered as part of an invasive strategy after fibrinolytic therapy. *(Level of Evidence: B)*

Immediately after successful fibrinolysis. Randomized prospective trials examined the efficacy and safety of immediate PCI after fibrinolysis (479,480,503). These trials

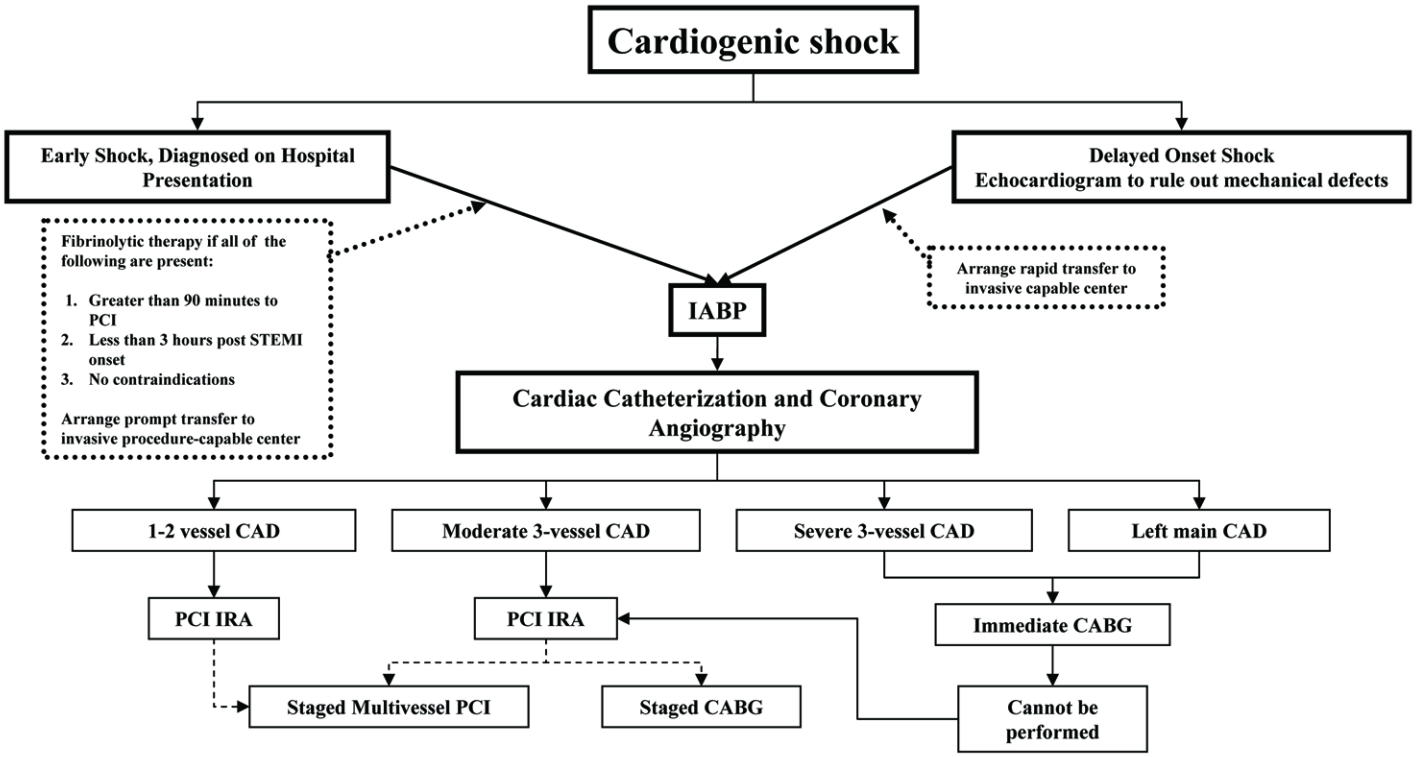


Figure 26. Recommendations for initial reperfusion therapy when cardiogenic shock complicates STEMI. Early mechanical revascularization with PCI/CABG is a class I recommendation for candidates less than 75 years of age with ST elevation or LBBB who develop shock less than 36 hours from STEMI and in whom revascularization can be performed within 18 hours of shock, and a class IIa recommendation for patients 75 years of age or older with the same criteria. Eighty-five percent of shock cases are diagnosed after initial therapy for STEMI, but most patients develop shock within 24 hours. An IABP is recommended when shock is not quickly reversed with pharmacological therapy, as a stabilizing measure for patients who are candidates for further invasive care. Dashed lines indicate that the procedure should be performed in patients with specific indications only. Recommendations for staged CABG and PCI are discussed in the text, as are definitions of moderate and severe 3-vessel CAD. PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; IABP = intra-aortic balloon pump; CAD, coronary artery disease; IRA = infarct-related artery; CABG = coronary artery bypass graft surgery; LBBB = left bundle-branch block. Modified with permission from Hochman. Circulation 2003;107:2998-3002 (502).

showed no benefit of routine PCI of the stenotic infarct-related artery immediately after fibrinolytic therapy. The strategy did not appear to salvage myocardium, improve LVEF, or prevent reinfarction or death. Those subjected to this approach appeared to have an increased incidence of adverse events, including bleeding, recurrent ischemia, emergency CABG, and death. These studies have not been repeated in the modern interventional era with improved equipment, improved antiplatelet and anticoagulant strategies, and coronary stents, thus leaving the question of routine PCI early after successful fibrinolysis unresolved in contemporary practice. Studies of facilitated PCI are presently enrolling patients (36,396,471,504).

Hours to days after successful fibrinolysis. It was initially suggested that elective PCI of the stenotic infarct-related artery hours to days after fibrinolysis might allow sufficient time for development of a more stable hemostatic milieu at the site of previous thrombotic occlusion. In this setting, PCI would be safer and more effective in reducing the incidence of reocclusion and improving survival. Two large randomized, prospective trials from an earlier PCI era tested this hypothesis, with both concluding that 1) there are fewer complications if PCI is delayed for several days after fibrinolytic therapy and 2) routine PCI in the absence of spontaneous or provocable ischemia does not improve LV function or survival (268,505-507). Thus, in unselected patients receiving fibrinolytic therapy, PCI of the stenotic infarct-related artery in the absence of evidence of recurrent ischemia within 48 hours did not appear to be beneficial.

Great improvements in equipment, operator experience, and adjunctive pharmacotherapy have increased PCI success rates and decreased complications. More recently, the invasive strategy for patients with NSTEMI has been given a Class I recommendation by the ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina/NSTEMI (4). Patients with STEMI are increasingly being treated similarly as an extension of this approach. Although 6 published reports (472,508-512) and 1 preliminary report (Lablanche JM; oral presentation, American Heart Association 2002 Annual Scientific Sessions, November 2002, Chicago, IL) support this strategy, randomized studies similar to those in NSTEMI need to be performed.

One study supports the policy of performing catheterization and subsequent revascularization for patients who do

have spontaneous or inducible angina after STEMI. The DANAMI trial (515) randomly assigned 1008 survivors of a first acute MI treated with fibrinolytic therapy within 12 hours of onset of symptoms to catheterization and subsequent revascularization or standard medical therapy if they showed evidence of spontaneous or inducible angina. Those who underwent revascularization had less unstable angina and fewer nonfatal MIs during a 2.5-year period of follow-up compared with those patients randomly assigned to medical treatment only (18% and 5.6% versus 30% and 10.5%, respectively).

Days to weeks after successful fibrinolysis. Continued thrombus lysis and remodeling of the infarct artery stenosis occur over the days to weeks after successful fibrinolysis, which makes the underlying residual coronary stenosis more stable and less prone to rethrombosis and reocclusion. Thus, delaying PCI for days to weeks after fibrinolysis might improve survival, even though earlier routine PCI does not. To date, there have not been adequately sized trials to evaluate this treatment strategy. Two older, small, randomized trials (516,517) demonstrated similar LV function, rates of reinfarction, and mortality in patients randomized to PCI or conservative therapy.

6.3.1.6.5. 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 VSR or mitral valve insufficiency.** ***(Level of Evidence: B)***
d. **Cardiogenic shock in patients less than 75 years old with ST elevation or 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 and 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 who 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)***

These recommendations are supplementary to those published recently in a more complete set of general guidelines and indications for CABG (518) and are restricted to patients with STEMI and associated complications. The basis for recommending surgery in emergency circumstances is the documented benefit of CABG for severe multivessel disease or left main coronary artery stenosis, particularly with reduced LV function (518-521), with the recognition that risk of emergency CABG is greater than that for elective operation.

The widespread use of fibrinolysis and primary PCI has largely superseded CABG for acute reperfusion of patients with STEMI. However, CABG still plays an integral role in the early reperfusion strategy for some patients. In the PAMI (Primary Angioplasty in Myocardial Infarction)-2 trial (522), of 1100 patients with MI and without cardiogenic shock, 5% underwent CABG as the primary reperfusion strategy with STEMI. Mortality was 6.4% if surgery was undertaken on an urgent or emergency basis versus 2.0% if elective. Major risk factors for death included poor LV function and advanced age. In the setting of cardiogenic shock complicating STEMI, emergency CABG has been used where other interventions have failed or have not been indicated. In the SHOCK registry (523), of 136 patients undergoing emergency CABG for cardiogenic shock due to LV failure, mortality was 27.9% compared to 45.5% in 268 patients undergoing PTCA. For patients undergoing CABG within 18 hours of the onset of shock, mortality was 39.6%. In a review of 25 papers reporting the outcome of CABG in 391 patients with cardiogenic shock, mortality was 35% (524). In GUSTO-I, mortality in a similar group of patients was 29% (98 of 340) after CABG and 29% (165 of 567) (422,525,526) after PTCA. On the basis of these studies, emergency CABG should only be considered for patients with STEMI with severe coronary artery disease. In the SHOCK trial, emergency CABG was performed at a median of 14 hours after

the onset of STEMI in 40% of those who underwent early revascularization; most of the patients undergoing CABG had significant left main or 3-vessel coronary artery disease. The 30-day mortality rate was similar to those with less severe coronary artery disease who underwent PTCA (42% versus 45%).

6.3.1.6.6. PATIENTS WITH STEMI NOT RECEIVING REPERFUSION. Many patients with suspected STEMI do not receive reperfusion therapy. For some of these patients, the lack of treatment represents a missed opportunity. For others, patient preference led to a decision that the clinical benefit was not worth the risk of the therapy. Other patients may have contraindications to treatment owing to comorbid disease. Few studies have examined the care and outcomes of patients with suspected STEMI who do not receive reperfusion therapy. Many of the studies (e.g., beta-blocker trials) that established therapies for MI patients preceded the reperfusion era, and so their efficacy in patients with STEMI who did not receive reperfusion is clear. The acute use of aspirin was shown to be effective in patients who did and did not receive fibrinolytic therapy. Guideline-based recommendations for nonreperfusion treatments should not vary whether or not patients received reperfusion therapy. The major difference is that patients not receiving reperfusion therapy are considered to have a higher risk for future adverse events (261). (See Section 6.3.1.6.8.1.2 for discussion of the TETAMI trial.)

6.3.1.6.7. 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)*

A high priority exists for the development of simple, accurate, readily available noninvasive techniques to assess the success of pharmacological reperfusion early, i.e., 60 to 90 minutes after administration of therapy. Prior studies evaluating clinical and ECG outcome measures of reperfusion used angiographic TIMI 2 or 3 flow as the "gold standard"; angiographic assessment of epicardial flow is now considered inadequate to completely assess myocardial perfusion. Indeed, it is now clear that microvascular perfusion may be impaired despite achievement of TIMI 3 flow and less than 50% coronary narrowing; moreover, abnormal microperfusion has negative prognostic implications (395,527,528).

Myocardial contrast echocardiography, myocardial angiographic perfusion with assessment of angiographic blush in the myocardium, and ECG assessment of ST resolution are recognized as useful techniques for assessing myocardial perfusion. The relatively simple and readily available evaluation of the ECG ST-segment resolution that exceeds 50% at 60 to 90 minutes after reperfusion is a good indicator of enhanced myocardial perfusion (527). This finding is also associated with enhanced recovery of LV function, reduced infarct size, and improved prognosis (277,349,395,529-531). In the TIMI-14 study of 888 patients, those with TIMI 3 perfusion and greater than 70% ST-segment resolution had substantial enhancement of survival compared with those without ST-segment resolution and angiographically patent infarct arteries (531).

Santoro and colleagues (532) evaluated 158 consecutive patients with STEMI referred for direct angioplasty within 6 hours of symptom onset. In their observational study of patients with TIMI grade 3 flow and less than 30% residual stenosis, 42 patients had less than 50% reduction in maximal ST elevation in a single lead versus 75 patients with at least 50% reduction in ST elevation. Those with ST-segment resolution had enhanced infarct-zone functional recovery and improved ejection fraction. The reduction of ST-segment elevation was the only independent predictor of functional recovery.

Persistence of unrelenting ischemic chest pain, absence of resolution of the qualifying ST-segment elevation, and hemodynamic or electrical instability are generally indicators of failed pharmacological reperfusion and the need to consider rescue PCI. Aggressive medical support may be necessary in the interim. (See Section 6.3.1.6.4.5.)

6.3.1.6.8. ANCILLARY THERAPY. Ancillary therapy plays a key role in the overall management of patients with STEMI and can be usefully categorized as conjunctive, in which case it facilitates and maintains coronary reperfusion, or adjunctive, which aims to limit the consequences of myocardial ischemia, enhance myocardial healing, and reduce the likelihood of recurrent events.

6.3.1.6.8.1. Antithrombins as Ancillary Therapy to Reperfusion Therapy

After rupture of a vulnerable or high-risk plaque, its contents are exposed to the passing bloodstream. Vulnerable plaques are laden with both lipid and collagen and are rich in tissue factor, thereby resulting in activation of the coagulation cascade, which ultimately results in the deposition of fibrin strands. In addition, platelets are activated and aggregate. Thrombin that is generated as a consequence of activation of the coagulation cascade is a pivotal molecule not only for the formation of fibrin strands but also for activation of platelets. Therefore, there is considerable rationale for ancillary therapy to inhibit the coagulation cascade in patients with STEMI, including both those who do and do not receive reperfusion therapy. The general term used to include agents that alter the function of 1 or more proteins in the coagulation cascade is antithrombins (533). However, such a broad term does not do justice to the biochemical complexities of agents that may

inhibit the coagulation cascade at multiple positions (e.g., UFH and LMWH) or in a single position (e.g., direct antithrombins). In addition to establishing and maintaining patency of the infarct-related artery, the rationale for prescribing antithrombins in selected patients with STEMI includes prevention of DVT, pulmonary embolism, LV mural thrombus formation, and cerebral embolization.

6.3.1.6.8.1.1. Unfractionated heparin as ancillary therapy to reperfusion therapy.

Class I

1. **Patients undergoing percutaneous or surgical revascularization should receive UFH. *(Level of Evidence: C)***
2. **Unfractionated heparin should be given intravenously to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase with dosing as follows: bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/hr (maximum 1000 U) initially adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds). *(Level of Evidence: C)***
3. **Unfractionated heparin should be given intravenously to patients treated with nonselective fibrinolytic agents (streptokinase, anistreplase, urokinase) who are at high risk for systemic emboli (large or anterior MI, atrial fibrillation (AF), previous embolus, or known LV thrombus). *(Level of Evidence: B)***
4. **Platelet counts should be monitored daily in patients taking UFH. *(Level of Evidence: C)***

Class IIb

It may be reasonable to administer UFH intravenously to patients undergoing reperfusion therapy with streptokinase. *(Level of Evidence: B)*

Despite the use of UFH (533) in STEMI for over 40 years, there is continued controversy regarding its role. In patients who are treated with fibrinolytic therapy, recommendations for UFH therapy depend on the fibrinolytic agent chosen. The nonspecific fibrinolytic agents (streptokinase, anistreplase, and urokinase) that produce a systemic coagulopathy, including depletion of factors V and VIII and massive production of fibrin(ogen) degradation products, are themselves anticoagulants. From this perspective, the need for conjunctive systemic anticoagulation with these agents conceptually is less compelling. However, the procoagulant potential of streptokinase, which induces extensive plasmin-mediated thrombin activity, has been noted as the rationale for antithrombotics (534). The rationale for UFH is clear for the more fibrin-specific agents, such as alteplase, reteplase, and tenecteplase. They induce less effect on the systemic coagulation system, and in many patients, very little breakdown of fibrinogen or depletion of coagulation factors is evident (535,536). Furthermore, the same procoagulant increase in thrombin activity is seen (534).

Over 60 000 patients were enrolled in the randomized ISIS-3 (357) and GISSI-2 (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico)/International (353,354) trials comparing subcutaneous UFH with no routine heparin in conjunction with streptokinase, anistreplase, and alteplase. During the period in which UFH was given, a small reduction in mortality (4 to 5 lives per 1000 treated) was observed in ISIS-3; however, by 30 days, the 2 to 3 lives saved per 1000 treated was no longer statistically significant. A small excess rate of hemorrhagic stroke (1 to 2 per 1000 treated patients) was observed together with a larger excess in systemic bleeding (3 to 5 per 1000 patients), although total stroke rate was not significantly increased. A meta-analysis of these and several smaller studies enrolling a total of 68 000 patients showed that 5 lives were saved per 1000 patients treated with UFH in addition to streptokinase (537). In the GUSTO-I trial (25), more than 20 000 patients treated with streptokinase were randomly assigned to routine intravenous versus routine subcutaneous UFH. No significant differences were observed in death, reinfarction, or nonhemorrhagic stroke rates, whereas excess rates of systemic bleeding and hemorrhagic strokes (trend) were observed in the intravenous UFH group. There was a 36% crossover rate from subcutaneous to intravenous UFH in this trial.

Several angiographic studies have evaluated coronary perfusion as a function of UFH therapy (538-540). More rapid resolution of ST-segment elevation has been reported in patients treated with intravenous UFH immediately at the time of streptokinase infusion than in those treated with intravenous heparin started at a later time, but the OSIRIS study (Optimization Study of Infarct Reperfusion Investigated by ST Monitoring) showed no difference in perfusion at 24 hours (539). In the GUSTO-I angiographic substudy, patients treated with intravenous UFH had an 88% patency rate at 5 to 7 days compared with a 72% rate in patients treated with subcutaneous UFH (p less than 0.05), although less reinfarction occurred in the subcutaneous UFH group (3.4% versus 4.0%, p less than 0.05) (538). When these angiographic studies are viewed as a whole, intravenous UFH appears to have no clinical advantage over subcutaneous administration when used with a nonspecific fibrinolytic agent, and the evidence for use of subcutaneous UFH is equivocal (541). There are few data comparing intravenous UFH to placebo.

The clinical importance of the procoagulant increase in thrombin activity after streptokinase administration is supported by the beneficial effect of newer antithrombins used in conjunction with streptokinase (see Section 6.3.1.6.8.1.3). The HERO (Hirulog and Early Reperfusion or Occlusion)-2 trial demonstrated reduced reinfarction with intravenous bivalirudin compared with intravenous UFH (33). The AMI-SK study demonstrated in patients treated with streptokinase improved ST-segment resolution at 180 minutes and higher rates of infarct-related artery patency at 8 days for enoxaparin compared with placebo. The composite of death, MI, and recurrent angina was reduced, but severe bleeding was increased (1.6% versus 0.8%), with no difference in ICH

(0% to 0.4%) (542). Additionally, a preliminary report of 5-year GUSTO-I follow-up data demonstrated similar survival rates for streptokinase with UFH versus alteplase-assigned patients. In the context of these new data and the event reduction (5 fewer deaths per 1000 patients) demonstrated in the meta-analysis (537), the recommendation for intravenous UFH administration with non–fibrin-specific fibrinolytic agents was changed from Class III to Class IIb.

When alteplase is the fibrinolytic agent, the empirical information to confirm the pathophysiological reasoning discussed above is primarily inferential. In a series of angiographic trials (543-545), intravenous UFH led to higher rates of infarct-related artery perfusion in conjunction with alteplase. A direct relation between duration of aPTT and the likelihood of infarct-related artery perfusion was observed (544,545). An overview (546) points out, however, that the effects of intravenous UFH on clinical outcomes from these studies are not so convincing; a significant increase in the rate of bleeding and nonsignificant increases in rates of reinfarction and hemorrhagic and nonhemorrhagic stroke are evident (546). These negative findings are tempered by a point estimate of an 18% reduction in mortality with broad confidence limits. Until the uncertainty is resolved, it appears judicious to use UFH for at least 48 hours with alteplase and to target the aPTT to 1.5 to 2.0 times control (approximately 50 to 70 seconds).

When primary PCI is chosen as the route of reperfusion, weight-adjusted boluses of heparin of 70 to 100 U/kg are recommended. This recommendation does not come specifically from empirical data in the setting of STEMI but from general observations in the setting of angioplasty that an activated clotting time of at least 250 to 350 seconds with the HemoTec device and 300 to 350 seconds with the Hemochron device is associated with a lower rate of complications than lower activated clotting times (432,547,548).

When GP IIb/IIIa antagonists are used (see Section 6.3.1.6.8.2.3), the UFH bolus should be reduced to 50 to 70 U/kg to achieve a target activated clotting time of 200 seconds with either the HemoTec or Hemochron device (432). UFH doses used during PCI for failed fibrinolysis should be similarly reduced and further lowered if used with GP IIb/IIIa antagonists as well.

The dose of UFH in the fibrinolytic-treated patient remains somewhat controversial. Given the infarct-related artery perfusion results just described, it would be reasonable to recommend an aPTT value more than 3-fold higher than the median control value. However, observational data strongly support a lower aPTT, because death, stroke, reinfarction, and bleeding were found to be lowest in the aPTT range of 50 to 70 seconds, or approximately 1.5 to 2.0 times the control value (549). Because of the evidence that the measured effect of UFH on the aPTT is important for patient outcome and that the predominant variable mediating the effect of a given dose of heparin is weight (549), it is important to administer the initial doses of UFH as a weight-adjusted bolus (541). For fibrin-specific (alteplase, reteplase, and tenecteplase) fibrinolytic-treated patients, a 60 U/kg bolus followed by a maintenance infusion of 12 U/kg/h (with a maximum of 4000 U bolus and 1000 U/h initial infusion for patients weighing more than 70 kg) is recommended. The recommended weight-adjusted dose of UFH, when it is administered without fibrinolytics, is a 60 to 70 U/kg IV bolus and a 12 to 15 U/kg/h infusion (4). Higher UFH doses are required for DVT and pulmonary embolism (80 U/kg and 18 U/kg/h) (550,551). Other factors that prolong aPTT include age, sex, and creatinine level. Elderly women may require lower bolus doses. Diabetics, smokers, and very heavy patients (weight more than 100 kg) may require higher UFH doses (550,552). When used with fibrinolytic therapy, an aPTT goal of 60 to 90 seconds is associated with an unacceptably high rate of ICH (359,553). The recommendation of an aPTT of 50 to 70 seconds was based on the GUSTO trials and supported by an overview of several fibrinolytic trials (325,380). ASSENT-3 was the first large-scale trial that used the recommended reduced-dose weight-adjusted UFH regimen (31). This regimen resulted in similar ICH rates but less bleeding than the higher dose used in ASSENT-2, without an increase in ischemic events. An aPTT measurement and dose adjustment are required beginning at 3 hours for those who receive UFH with fibrinolytics (28). The aPTT should be remeasured 6 hours after each dose adjustment until it is in the target range and daily thereafter. There is wide variability in aPTT measurement between laboratories, and it is not known what UFH level, as measured by anti-Xa activity, corresponds with an aPTT of 50 to 70 seconds. However, for most thromboplastin reagents, this corresponds to 0.2 to 0.5 U/mL heparin by anti-Xa activity.

Once UFH has been started, the appropriate duration of therapy is uncertain. The only randomized trial to address this issue found that discontinuation of UFH after 24 hours after fibrinolytic therapy with alteplase resulted in no measurable increase in ischemic events (554), although this study did not have adequate power to detect modest differences. A reasonable approach is to use intravenous UFH for 48 hours and then to use UFH according to the clinical characteristics of the patient. UFH may be discontinued in low-risk patients, given subcutaneously in patients at high risk of systemic embolization, and given intravenously in patients at high risk for coronary reocclusion.

There is concern that when UFH is discontinued abruptly, the patient undergoes a high-risk period for recurrent thrombosis (heparin rebound) because of increased thrombin activity (555,556). Despite this concern, no specific policy has been tested to attempt to reduce this clinical rebound effect. Several ongoing studies, however, are reducing UFH infusions in a gradual fashion (e.g., by half within 6 hours, then discontinuing over the subsequent 12 hours).

Platelet counts should be monitored daily in patients being treated with UFH. Evidence suggests the incidence of heparin-induced thrombocytopenia is 3% and that this is associated with a substantial risk of prothrombotic events (557). If the platelet count drops below 100 000, a test for heparin-induced thrombocytopenia should be obtained, and the clinician should be vigilant for thrombotic complications,

because the prognosis in patients with thrombocytopenia is substantially worse (558).

6.3.1.6.8.1.2. Low-molecular-weight heparin as ancillary therapy to reperfusion therapy.

Class IIb

Low-molecular-weight heparin might be considered an acceptable alternative to UFH as ancillary therapy for patients aged less than 75 years who are receiving fibrinolytic therapy, provided that significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women) is not present. Enoxaparin (30-mg IV bolus followed by 1.0 mg/kg SC every 12 hours until hospital discharge) used in combination with full-dose tenecteplase is the most comprehensively studied regimen in patients aged less than 75 years of age. *(Level of Evidence: B)*

Class III

1. **Low-molecular-weight heparin should not be used as an alternative to UFH as ancillary therapy in patients aged more than 75 years who are receiving fibrinolytic therapy. *(Level of Evidence: B)***
2. **Low-molecular-weight heparin should not be used as an alternative to UFH as ancillary therapy in patients less than 75 years who are receiving fibrinolytic therapy but have significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women). *(Level of Evidence: B)***

There have been no definitive phase III randomized trials of LMWH in patients with STEMI to provide a firm basis for recommendations. However, a number of phase II clinical trials provide encouraging information that suggests that LMWH may be an attractive alternative to UFH. These clinical trials include those with LMWH as ancillary therapy to fibrinolysis and those in patients not receiving fibrinolysis (31,158,542,559-567). These 2 broad categories of trials with LMWH involve either enoxaparin or dalteparin, the 2 LMWHs studied most extensively in patients with STEMI. Clinical evaluation of LMWH as ancillary therapy to most of the commonly prescribed fibrinolytics has been reported with the exception of reteplase (Table 19) (31,158,542,559-567).

The available data suggest that the rate of early (60 to 90 minutes) reperfusion of the infarct artery either assessed angiographically or by noninvasive means is not enhanced by administration of a LMWH. However, a generally consistent theme of a lower rate of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events emerges in patients receiving LMWH regardless of whether the control group was given placebo or UFH.

The most comprehensive data available are from the ASSENT-3 trial, in which patients received tenecteplase and either UFH (bolus 60 U/kg; initial infusion 12 U/kg/h; duration of treatment equals 48 hours) or enoxaparin (bolus 30 mg; subcutaneous injections 1.0 mg/kg every 12 hours; duration of treatment equals duration of hospital stay) (31). Each of the elements of the composite end point of 30-day mortality, in-hospital reinfarction, or in-hospital recurrent ischemia were reduced with enoxaparin treatment. This was associated with a slight, nonsignificant increase in noncerebral bleeding complications. In patients aged more than 75 years, the rate of noncerebral major bleeds was 4.1% with UFH and 7.2% with enoxaparin. Patients with significant renal dysfunction (serum creatinine greater than 2.5 mg/dL for men and greater than 2 mg/dL for women) were excluded from ASSENT-3, and therefore enoxaparin cannot be recommended for use in combination with tenecteplase in patients with severe renal dysfunction until more data are available. At 1 year, no difference was noted in the composite end point noted above between the UFH and enoxaparin groups in ASSENT-3 (31).

However, results from the third Assessment of the Safety and Efficacy of a New Thrombolytic PLUS (ASSENT-3 PLUS) trial underscore the need for continued evaluation of the safety of LMWH as an adjunct to fibrinolysis (158). Among 1639 patients with STEMI receiving tenecteplase and either enoxaparin or UFH in a prehospital setting, higher rates of both major bleeding (4.0% versus 2.8%; p equals 0.18) and ICH (2.2% versus 1.0%; p equals 0.05) were seen in the enoxaparin group than in the UFH group. There was a significant interaction between patient age and risk of bleeding because almost all cases of excess ICH were confined to patients older than 75 years (158,568). The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction - Study 25 (EXTRACT-TIMI-25) trial is evaluating enoxaparin versus UFH in patients receiving fibrinolytic therapy and will provide information on the efficacy and safety of reduced doses of enoxaparin in the elderly.

The combination of tirofiban and enoxaparin was studied in 1224 patients presenting with STEMI in the Treatment of Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) trial (566). Patients ineligible for fibrinolysis were randomized in a 2×2 fashion to receive either enoxaparin (intravenous 30 mg bolus and subcutaneous injection of 1 mg/kg twice daily) or UFH (intravenous 70 U/kg bolus and 15 U/kg/h infusion) with or without tirofiban (intravenous 10 mcg/kg bolus and 0.1 mcg/kg/min infusion) for 2 to 8 days. There were no differences noted in the primary efficacy end point (30-day combined incidence of death, reinfarction, or recurrent angina) between either enoxaparin and UFH monotherapy groups (15.4% versus 17.3%) or between enoxaparin and UFH combination groups (16.1% versus 17.2%). Major bleeding was rare and not statistically different among all 4 groups.

6.3.1.6.8.1.3. Direct antithrombins as ancillary therapy to reperfusion therapy.

Class IIa

In patients with known heparin-induced thrombocytopenia, it is reasonable to consider bivalirudin as a useful alternative to heparin to be used in conjunction with streptokinase. Dosing according to the HERO 2

Table 19. Trials of Low-Molecular Weight Heparin in Patients With ST-Elevation Myocardial Infarction

	Trial (Reference)	No.	Fibrinolytic	Control	LMWH Dose	End Point	Control, %	LMWH, %
Ancillary therapy to fibrinolysis:								
Enoxaparin	HART II (559)	400	tPA	UFH 5000 U bolus; 15 U/kg/h infusion for at least 72 h	30 mg IV bolus; 1 mg/kg SC every 12 h for at least 72 h	90-min TIMI 3 flow grade	48	53
						Reocclusion of initially patent IRA by 1 wk	9.8	5.9
						TIMI major hemorrhage	3.0	3.6
						30-day mortality	5.0	4.5
	AMI SK (542)	49	SK	Placebo	30 mg IV bolus; 1 mg/kg SC every 12 h for 5-8 days	Complete ST-segment resolution at 180 min	25	36
						Patent IRA at angiography at 8 d (p = 0.001)	72	88
						Rate of death/recurrent MI/recurrent angina through 30 days (p=0.03)	21.0	13.4
						Recurrent MI	7.4	2.4
	BAIRD (560)	300	SK, APSAC, tPA	UFH (5000 U IV bolus, then 30 000 U per 24 h)	40 mg IV bolus; 40 mg SC every 8 h for 4 days	Death, reinfarction, or readmission with unstable angina at 90 days (p = 0.04)	36.4	25.5
						Cardiac death	10.6	6.0
						Reinfarction	19.9	14.8
						Readmission with unstable angina	6.0	4.7
						Clinically significant hemorrhage	4.0	3.0
	ASENOX (561)	312	SK (1.5 MU over 20 min)	UFH 1,000 U/h for 48-72 h	40 mg IV bolus; 1 mg/kg SC every 12 h for 48-72 h	Early noninvasive signs	76	80
						Rate of noninvasive signs of of reperfusion reocclusion through 30 days	6.3	2.6
	ENTIRE-TIMI 23 (562)	483	TNK	UFH (bolus 60 U/kg; infusion 12 U/kg/h) for patients receiving full-dose TNK; UFH (bolus 40 U/kg; infusion 7 U/kg/h) for patients receiving half-dose TNK plus abciximab	1 mg/kg SC every 12 h either with or without initial 30 mg IV bolus in full-dose TNK group. Dose ranging from 0.3 to 0.75 mg/kg SC every 12 h either with or without initial IV bolus of 30 mg in patients receiving half-dose TNK plus abciximab	Mortality	8.2	7.14
						TIMI 3 flow rate at 60 min	50	51
						Death or recurrent MI through 30 days (p = 0.005)		
						with full-dose TNK	15.9	4.4
						with combination therapy	6.5	5.5
						TIMI major hemorrhage		
						with full-dose TNK	2.4	1.9
						with combination therapy	5.2	8.5

Continued on next page

Table 19. *Continued*

	Trial (Reference)	No.	Fibrinolytic	Control	LMWH Dose	End Point	Control, %	LMWH, %
Ancillary therapy to fibrinolysis (continued):								
	ASSENT-3 (31)	6095*	TNK	UFH IV bolus of 60 U/kg (maximum 4000 U), initial infusion of 12 U/kg/h (maximum 1000 U/h) for a minimum of 48 h	30 mg IV bolus, 1 mg/kg SC q 12 h until hospital discharge or successful revascularization (maximum 7 days)	30-day mortality, inhospital reinfarction, or inhospital refractory ischemia	15.4	11.4
						30-day mortality	6.0	5.4
						Inhospital reinfarction	4.2	2.7
						Inhospital refractory ischemia	6.5	4.6
						Major bleeding other than ICH	2.2	3.0
	ASSENT-3 PLUS (158)	1639	TNK	UFH IV bolus of 60 U/kg (maximum 4000 U), initial infusion of 12 U/kg/h (maximum 1000 U/h) for a minimum of 48 h	30 mg IV bolus, 1 mg/kg SC q 12 h until hospital discharge or successful revascularization (maximum 7 days)	30-day mortality, inhospital reinfarction, or inhospital refractory ischemia (p = 0.08)	17.4	14.2
						Major bleeding	2.8	4.0
						ICH (p = 0.05)	1.0	2.2
						ICH in patients greater than or equal to 75 years old	0.78	6.71
Dalteparin	ASSENT-PLUS (563)	439	tPA	UFH	120 IU/kg q 12 h for 4-7 days	TIMI 3 flow at median of 6 days	62.5	69.35
						30-day mortality	5.25	4.1
						In-hospital reinfarction (p = 0.01)	5.4	1.4
	FRAMI (564)	517	SK	Placebo		LV thrombus or arterial embolism (p=0.03)	22	14
						Major hemorrhage (p = 0.006)	0.3	2.9
	BIOMACS II (565)	101	SK	Placebo		TIMI 3 flow at 20-28 hours	51	68
						Ischemic episodes 6-24 h after start of Rx (p = 0.04)	38	16
LMWH in patients not receiving fibrinolysis:								
Enoxaparin	TETAMI (566)	1224		Enoxaparin 30 mg IV bolus; 1 mg/kg SC BID for 2-8 days	30 mg IV bolus; 1 mg/kg SC BID + tirofiban 10 mcg/kg IV and 0.1 mcg/kg/min infusion for 2-8 days	Death, MI, or recurrent angina at 30 days†	15.4	16.1
						Death, recurrent MI†	8.7	8.5
						Major hemorrhage (TIMI)‡	1.0	2.0
						Hemorrhagic stroke‡	0.0	0.3
				UFH 70 U/kg bolus; 15 U/kg/h IV for 2-8 days	UFH 70 U/kg bolus; 15 U/kg/h IV + tirofiban 10 mcg/kg IV and 0.1 mcg/kg/min infusion for 2-8 days	Death, MI, or recurrent angina at 30 days†	17.3	17.2
						Death, recurrent MI†	9.2	8.0
						Major hemorrhage (TIMI)‡	1.0	1.6
						Hemorrhagic stroke‡	0.0	0.3
Dalteparin	FAMI (567)	1178		Placebo	Open label dalteparin 120 IU/kg twice daily for 1-3 days followed by double-blind dalteparin 7500 IU (or placebo) for 30 days	Death, MI, or recurrent angina, emergency revascularization	6.7	7.0

LMWH = low-molecular weight heparin; tPA = alteplase; IV = intravenous; TIMI = Thrombolysis in Myocardial Infarction; UFH = unfractionated heparin; h = hour; IRA = infarct-related artery; wk = week(s); SC = subcutaneous; SK = streptokinase; min = minute(s); d = day(s); MI = myocardial infarction; APSAC = anistreplase; MU = mega units; TNK = tenecteplase; No. = number; ICH = intracranial hemorrhage; LV = left ventricular; BID = twice a day.
*UFH = 2038; enoxaparin = 2040; half-dose TNK plus abciximab plus reduced-dose UFH = 2017.
†Randomized patients.
‡Treated patients.

regimen (a bolus of 0.25 mg/kg followed by an intravenous infusion of 0.5 mg/kg/h for the first 12 hours and 0.25 mg/kg/h for the subsequent 36 hours) (33) is recommended, but with a reduction in the infusion rate if the partial thromboplastin time is above 75 seconds within the first 12 hours. *(Level of Evidence: B)*

A number of direct thrombin inhibitors are now available for use in heparin-induced thrombocytopenia and DVT but have not yet been approved for the treatment of acute coronary syndrome (Table 20) (39,359,368,382,383,553,569-573). One, (bivalirudin) has been approved for use in patients with unstable angina undergoing PCI. A meta-analysis evaluated 11 trials that collectively enrolled more than 35 000 patients, comparing direct thrombin inhibitors with UFH (39). There was an approximately 25% reduction in the incidence of MI in patients with STEMI treated with either hirudin or bivalirudin, but there was less evident efficacy for univalent thrombin inhibitors (argatroban, efegatran, and inogatran). Major bleeding was reduced with bivalirudin compared with heparin (4.2% versus 9.0%; OR 0.44 [0.34 to 0.56]). There was an excess of bleeding after the use of hirudin and no difference with univalent inhibitors; statistical heterogeneity among these 3 groups of trials existed (39).

Subsequent to the meta-analysis, a large phase 3 study (HERO-2) of 17 073 patients with STEMI who presented within 6 hours of onset of chest pain was performed to evaluate the efficacy of bivalirudin versus UFH administered in conjunction with streptokinase (33). In the HERO-2 trial, bivalirudin did not reduce mortality compared with UFH (10.8% versus 10.9%) but was associated with a lower rate of adjudicated myocardial reinfarction within 96 hours (1.6% versus 2.3%, p equals 0.005). Although it was anticipated there would be fewer hemorrhagic complications with bivalirudin, severe bleeding occurred in 0.7% of the bivalirudin group versus 0.5% for heparin (p equals 0.07), and intracerebral bleeding occurred in 0.6% versus 0.4% (p equals 0.09), respectively, possibly related to higher aPTT levels in the bivalirudin group. The frequency of moderate and mild bleeding was also greater with bivalirudin (33,323).

Bivalirudin is currently indicated only for anticoagulation in patients with unstable angina who are undergoing percutaneous coronary angioplasty (574). On the basis of the data in the HERO-2 trial, the Writing Committee believes that bivalirudin could be considered an acceptable alternative to UFH in those patients with STEMI who receive fibrinolysis with streptokinase, have heparin-induced thrombocytopenia, and who, in the opinion of the treating physician, would benefit from anticoagulation.

6.3.1.6.8.1.4. Other.

A phase 2 angiographic trial Pentasaccharide as an Adjunct in ST-Segment Myocardial Infarction (PENTALYSE) evaluated fondaparinux, a synthetic pentasaccharide that is a highly selective inhibitor of factor Xa. Fondaparinux selectively binds antithrombin III, inducing a conformational change that increases the anti-Xa activity of antithrombin III more than 300 times, which results in dose-dependent inhibition of factor Xa (575). A total of 333 patients with evolving STEMI were treated with aspirin and alteplase and randomized to UFH given intravenously for 48 to 72 hours or to a low, medium, or high dose of fondaparinux. The percentage of patients achieving TIMI grade 3 flow at 90 minutes was 68% in the UFH control group and ranged between 60% and 69% with fondaparinux. Thus, selective factor Xa inhibition appears to be an attractive therapeutic concept in patients presenting with STEMI; however, further study is required before it can be recommended for routine administration.

6.3.1.6.8.2. Antiplatelets

6.3.1.6.8.2.1. Aspirin.

Class I

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)*

As discussed in Section 7.4.4 and Section 6.3.1.4, aspirin should be given to the patient with suspected STEMI as early as possible and continued indefinitely, regardless of the strategy for reperfusion and regardless of whether additional antiplatelet agents are administered. True aspirin allergy is the only exception to this recommendation.

6.3.1.6.8.2.2. Thienopyridines.

Class I

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

Class IIa

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)*

Ticlopidine and clopidogrel are ADP-receptor antagonists and are quite similar chemically. Ticlopidine can cause neutropenia and thrombotic thrombocytopenia. Clopidogrel is preferred because of fewer side effects, lack of need for laboratory monitoring, and once-daily dosing. Clopidogrel combined with aspirin is recommended for patients with STEMI who undergo coronary stent implantation (576-580). There are no safety data available regarding the combination of fib-

Table 20. Trials of Direct Thrombin Inhibitors Used as Ancillary Therapy in Patients With ST-Elevation Myocardial Infarction

Direct Thrombin Inhibitor	Trial (Reference)	n	Fibrinolytic	Control/Ref. Arm(UFH)	Direct Thrombin Inhibitor	End Point(s)	UFH	Direct Thrombin Inhibitor
Hirudin	TIMI 5 (569)	246	rtPA	UFH 5000 U bolus; 1000 U/h IV to PTT 65-90 sec for 5 days	4 Ascending doses; bolus 0.15-0.6 mg/kg followed by fixed infusion 0.05-0.2 mg/kg for 5 days	TIMI 3 flow at 90 min & 18-36 h (without death or re-MI) (p=0.07)	49.4%	61.8%
						Reocclusion (p=0.07)	6.7%	1.6%
						Death/reinfarction (p=0.02)	16.7%	6.8%
						Major hemorrhage (p=0.09)	4.7%	1.2%
	GUSTO IIa (359)	1264	rtPA or SK	5000 U bolus & 1000 -1300 U/h to PTT 60-90 sec	0.6 mg/kg bolus & 0.2 mg/kg/h infusion without PTT adjustment	Death or MI within 30 days		
						Major hemorrhage		
						ICH*	1.5%	2.2%
						[95% CI]	(0.5-2.4)	(1.0-3.3)
						*Early termination of trial due to excess ICH		
	TIMI 9a (553)	757	rtPA or SK	5000 U bolus & 1000-1300 U/h to PTT 60-90 sec	0.6 mg/kg bolus followed by 96-h infusion of 0.2 mg/kg/h	Death/re-MI		
						CHF		
						Shock		
						LVEF less than 0.40		
						ICH or major hemorrhage	1.9%	1.7%
						[95% CI]	(0.8-3.9)	(0.5-3.7)
						Spontaneous hemorrhage (p=0.02)	3.0%	7.0%
						[95% CI]	(1.5-5.3)	(4.5-10.2)
						*DSMB requested early termination		
	HIT III (368)	302	rtPA	70 U/kg bolus & 15 U/kg/h	0.4 mg/kg bolus & 0.15 mg/kg/h (48-72 h duration)	Death/reinfarction at 30 days	0%	3.4%
						*Early termination due to excess ICH in hirudin group, i.e., 5 of 148 patients (3.4%)		
	TIMI 9B (382)	3002	rtPA or SK	5000 U followed by 1000/h; PTT 55-85 sec for 96 h	0.5 mg/kg bolus; infusion 0.1 mg/kg/h for 96 h	Unsatisfactory outcome, i.e., death, re-MI, CHF, shock, and major bleeding OR 1.02 [95% CI 0.80-1.31]	9.5%	9.7%
						ICH (p=NS)	0.9%	0.4%
						Major hemorrhage (p=NS)	1.1%	1.8%
	GUSTO IIb (383)	4131	rtPA or SK	5000 U followed by 1000 U/h and 75 + 29 hours (SD)	0.1 mg/kg bolus followed by infusion of 0.1 mg/kg/h 75 + 29 hours (SD)	Death/re-MI at 30 days OR 0.86 [95% CI 0.70-1.05]	11.3%	9.9%
						ICH	0.4%	0.5%
						Severe bleeding	1.5%	1.1%

Continued on next page

Table 20. *Continued*

Direct Thrombin Inhibitor	Trial (Reference)	n	Fibrinolytic	Control/Ref. Arm(UFH)	Direct Thrombin Inhibitor	End Point(s)	UFH	Direct Thrombin Inhibitor	
	HIT 4 (572)	1208	SK	12 500 U SC every 12 h for 5-7 days	0.2 mg/kg IV bolus & 0.5 mg/kg twice a day SC for 5-7 days	TIMI 3 patency at 90 min (p = 0.16)	33.5%	40.7%	
						ST resolution at 90 min (p = 0.05)	22%	28%	
						Composite clinical end point (p = NS)	24.3%	22.7%	
						ICH (p = NS)	0.3%	0.2%	
						Major bleeding	3.5%	3.3%	
						Death, nonfatal stroke Re-MI, PCI, or refractory angina at 30 days	47%	77%	
Hirulog	Pilot - hirulog streptokinase (570)	45	SK	1000 U/h to PTT 2.0-2.5 × control for 4.7 days	0.5 mg/kg/h for 12 hours & then 0.1 mg/kg/h for 4.7 days	TIMI 2 or 3 flow at 90 min (p less than 0.05)	27%	13%	
						Serious bleeding (p = NS)	8%	0%	
						Absence reocclusion (p = NS)		0.5 mg/kg/h	1.0 mg/kg/h
	Hirulog vs heparin in STEMI (571)	70	SK	5000 U bolus & 1000 U/h	0.5 mg/kg bolus - 1.0 mg/kg for 12 h - at 12 h, dose reduction to 0.1 mg/kg/h or placebo for 4-6 days (4:1 random-ization)		46% (n=13)	96% (27)	79% (28) 4/28
						TIMI 2/3 flow 90 min post-SK	0/13	1/27	
						Reocclusion	4/13		5/28
						Serious bleeding		6/27	
							Plus rtPA	Plus SK	
Efegatran	ESCALAT (573)	245	SK & rtPA	5000 U bolus followed by 1000 U/h with rtPA	4 Ascending doses; 0.05 mg/kg - 0.2 mg/kg bolus, infusion 0.3-1.0 mg/kg/h; for 72-96 h with 1.5 MU SK		53%	40%	
						TIMI 3 flow at 90 min (p = 0.10)	7%	15%	
						Composite clinical end point (p = 0.14)	11%	23%	
						Major bleeding (p = 0.07)	0%	0%	
						ICH	6.9%	6.3%	
Meta-analysis: hirudin bivalirudin argatroban efegatran inogatran	Direct thrombin inhibitor trialists' (39) (5 trials with ST elevation)	9947	SK & rtPA	UFH		Death or MI at 30-days OR = 0.91 [95% CI 0.77-1.06]	3.4%	2.5%	
						MI OR = 0.75 [95% CI 0.59-0.94]	3.3%	2.9%	
						Major bleeding OR = 0.89 [95% CI 0.71-1.11]			

UFH = unfractionated heparin; rtPA = recombinant alteplase; U = unit; min = minutes; TIMI = Thrombolysis in Myocardial Infarction; h = hours; IV = intravenous; PTT = prothrombin time; re-MI = recurrent myocardial infarction; sec = seconds; SK = streptokinase; ICH = intracranial hemorrhage; CI = confidence interval; CHF = congestive heart failure; LVEF = left-ventricular ejection fraction; DSMB = Data Safety Monitoring Board; OR = odds ratio; SD = standard deviation; SC = subcutaneous; NS = not significant; PCI = percutaneous coronary intervention; MU = mega units.

rinolytic agents and clopidogrel, but ongoing trials will provide this information in the future. However, in patients in whom aspirin is contraindicated because of aspirin sensitivity, clopidogrel is probably useful as a substitute for aspirin to reduce the risk of occlusion (581). There are no safety data comparing 300 and 600 mg as loading doses for clopidogrel. We do not recommend routine administration of clopidogrel as pretreatment in patients who have not yet undergone diagnostic cardiac catheterization and in whom CABG surgery would be performed within 5 to 7 days if warranted (431).

6.3.1.6.8.2.3. 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)*

The use of intravenous GP IIb/IIIa receptor inhibitors in combination with fibrinolytic agents is discussed in Section 6.3.1.6.3.8. Intravenous GP IIb/IIIa receptor inhibitors have also been studied as supportive antiplatelet therapy in patients undergoing PCI. Five randomized trials compared abciximab to placebo control in a collective total of 3666 patients undergoing primary PCI for STEMI (34-36,38,582). A total of 1843 patients received abciximab, a relatively small data set on which to base recommendations for treatment. In addition, in the setting of primary PCI, periprocedural recurrent MI is not easily measured, so the benefit of antiplatelet therapy with GP IIb/IIIa inhibitors is harder to determine. Finally, only 1 of the trials, CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications), provided data on the effect of abciximab on patients who underwent PTCA without stenting and on patients who had a stent implanted at the time of PCI (38).

The ADMIRAL study (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up) (36) enrolled 300 patients with STEMI undergoing primary stenting; half received placebo and half received abciximab in the mobile intensive care unit or the ED before arrival at the catheterization laboratory. Abciximab-treated patients had higher infarct-artery patency (TIMI 2/3 flow) rates (25.9% versus 10.8%) before revascularization and a better LVEF (0.61 versus 0.57) 6 months after revascularization. Abciximab-treated patients had a lower rate of death, reinfarction, or need for subsequent target-vessel revascularization at 30 days (6.0% versus 14.6%, p equals 0.01) and at 6 months (7.4% versus 15.9%, p equals 0.02); the majority of the benefit of abciximab on the composite primary end point in ADMIRAL was driven by a reduction in urgent target-vessel revascularization. The CADILLAC study (38) enrolled 2082 patients (88% with STEMI) undergoing primary PTCA or stenting; half received placebo, and half were treated with abciximab in the catheterization laboratory. At 30 days, the incidence of the primary composite end point of death, reinfarction, revascularization, or disabling stroke was highest in the group assigned to receive PTCA alone (8.3%), and the lower rates in the other 3 groups were not significantly different from one another (4.8% PTCA plus abciximab, 5.7% stenting alone, 4.4% stenting plus abciximab). The Anticoagulation for Cardioversion using Enoxaparin (ACE) study (582) randomized 400 patients to stenting alone or stenting plus abciximab (administered immediately before the procedure). At 30 days, the incidence of the primary composite end point of death, reinfarction, target-vessel revascularization, or stroke was reduced in the stent-plus-abciximab group (4.5%) versus the stent-alone group (10.5%; p equals 0.023); the majority of the benefit of abciximab on the primary end point in the ACE study was driven by a reduction in the rate of reinfarction. It is unclear whether the different 30-day results in the studies described above are related to patient selection and risk, timing of abciximab administration, or patency rates before revascularization (583). Assessment of the benefit of abciximab at 6 months varies depending on the composite end point, with evidence in favor of its use derived from composite end points of death/reinfarction or death/reinfarction/urgent target-vessel revascularization, whereas evidence of long-term benefit of abciximab is lost if elective revascularization is added to the end point (34,36,583).

The Writing Committee believes that it is reasonable to start treatment with abciximab as early as possible in patients undergoing primary PCI (with or without stenting), but given the size and limitations of the available data set, assigned a Class IIa recommendation. The data on tirofiban and eptifibatide in primary PCI are far more limited than for abciximab. However, given the common mode of action of the agents, a modest amount of angiographic data (584), and general clinical experience to date, tirofiban or eptifibatide may be useful as antiplatelet therapy to support primary PCI for STEMI, with or without stenting (Class IIb recommendation).

6.3.1.6.9. Other Pharmacological Measures.

6.3.1.6.9.1. Inhibition of Renin-Angiotensin-Aldosterone System

Class I

1. **An 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 (5 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)***

A number of large, randomized clinical trials have assessed the role of ACE inhibitors early in the course of acute MI. All trials in which ACE inhibitors were administered orally demonstrated a benefit in mortality. In the ISIS-4 trial, 58 000 patients with suspected acute MI were randomly assigned within the first 24 hours (median 8 hours) to receive either oral captopril or placebo; a significant 7% relative reduction was observed in 5-week mortality among those randomly assigned to captopril (absolute difference of 4.9 fewer deaths per 1000 patients treated for 1 month) (152). The largest benefit was among those with an anterior infarction. Among the 143 fewer deaths in the group allocated captopril, 44 occurred in days 0 through 1 and 37 in days 2 through 7 (585), which demonstrates that early therapy is important. In the GISSI-3 trial, more than 19 000 patients with either ST-segment elevation or depression were randomly assigned to lisinopril or open control (586). There was a significant reduction in 6-week mortality (OR 0.88; 95% CI 0.79 to 0.99); 60% of the lives were saved during the first 5 days of treatment. The SMILE (Survival of Myocardial Infarction: Long-Term Evaluation) study involved 1556 patients randomly assigned within 24 hours to receive either placebo or zofenopril (587). The patient population was restricted to those with anterior MI who had not received fibrinolytic therapy. Use of an early ACE inhibitor in this trial suggested a trend of more lives saved in the first 6 weeks (RRR 25%, p equals 0.19). A Chinese captopril study involving more than 13 600 patients with suspected acute MI also revealed an approximate 0.5% absolute mortality benefit among those who were randomly assigned to the ACE inhibitor compared with the control population (588). A meta-analysis of these major trials along with 11 smaller trials that collectively enrolled more than 100 000 patients revealed a 6.5% overall odds reduction (p equals 0.006) with an absolute benefit of 4.6 fewer deaths per 1000 patients treated among those who received the ACE inhibitor (585). These data conclusively support a role for ACE inhibitors in the early and convalescent phases of STEMI.

All trials with oral ACE inhibitors have shown benefit from its early use, including those in which early entry criteria included clinical suspicion of acute infarctions. Data from these trials indicate that ACE inhibitors should generally be started within the first 24 hours, ideally after fibrinolytic therapy has been completed and blood pressure has stabilized. ACE inhibitors should not be used if systolic blood pressure is less than 100 mm Hg or less than 30 mm Hg below baseline, if clinically relevant renal failure is present, if there is a history of bilateral stenosis of the renal arteries, or if there is known allergy to ACE inhibitors.

The meta-analyses of the large ACE inhibitor trials have been useful in defining those patient subgroups most likely to demonstrate the greatest benefit from early post-MI ACE inhibitor therapy. According to a meta-analysis of nearly 100 000 randomized patients, the benefits of early oral ACE inhibitors are greatest among those aged 55 to 74 years, with an anterior infarct, and with a heart rate of 80 bpm or higher (589).

ACE inhibitor therapy after STEMI should start with low-dose oral administration and increase steadily to achieve a full dose within 24 to 48 hours. For example, in ISIS-4, an initial 6.25-mg dose of captopril was given and, if tolerated, was followed by 12.5 mg 2 hours later, 25 mg 10 to 12 hours later, and then 50 mg twice per day. GISSI-3 patients received 5 mg or oral lisinopril at the time of randomization, 5 mg after 24 hours, 10 mg after 48 hours, and then 10 mg daily for 6 weeks or open control. Similar graded-dose schedules should be used with other ACE inhibitors such as ramipril, zofenopril, enalapril, and quinapril. Regarding the potential for aspirin to blunt the effect of ACE inhibitors, the Writing Committee thought that any adverse drug interaction between aspirin and ACE inhibitors was of a small magnitude and was far outweighed by the benefit of the combined administration of both drugs to patients recovering from STEMI (430,590,591). Lower doses of aspirin are likely to minimize any potential interaction.

Finally, the only trial that did not show a benefit with ACE inhibitors was the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II, in which patients were randomly assigned within the first day to receive either intravenous enalaprilat or placebo followed by increasing oral dosages of either enalapril or placebo (592). This trial was terminated early by its Safety Committee because of the high probability that a significant benefit of enalapril over placebo was unlikely to be demonstrated with continuation of the trial, as well as concern over an adverse effect among elderly patients who experienced an early hypotensive reaction. The 95% confidence limits ranged from showing a 7% benefit to 29% harm. Thus, intravenous enalaprilat should be avoided.

The use of ARBs has not been explored as thoroughly as ACE inhibitors in patients with STEMI. However, clinical experience in the management of patients with heart failure and data from clinical trials in patients with STEMI (see

Sections 7.4.3 and 7.6.4) suggest that ARBs may be useful in patients with depressed LV function or clinical heart failure who are intolerant of an ACE inhibitor. Use of aldosterone antagonists in patients with STEMI is discussed in Sections 7.4.3 and 7.6.4.

6.3.1.6.9.2. Metabolic Modulation of the Glucose-Insulin Axis

Metabolic modulation of patients with STEMI was originally proposed by Sodi-Pallares et al. (593) in 1962. A meta-analysis of 1932 patients in trials conducted between 1965 and 1987 demonstrated a 28% relative mortality reduction, with an absolute benefit of 49 lives saved per 1000 patients treated (Table 21) (594-597). Subsequent trials in the reperfusion era show promising but variable results. High-dose infusions of glucose-insulin-potassium (GIK) (25% glucose, 50 IU/L soluble insulin, and 80 mmol/L KCl at a rate of 1.5 mL/kg/h for 24 hours) or a low-dose infusion (10% glucose, 20 IU/L soluble insulin, and 40 mmol/L KCl at a rate of 1 mL/kg/h for 24 hours) were compared to usual care. The ECLA (Estudios Cardiológicos Latinoamérica) pilot suggested a relationship between the time from symptom onset and impact of GIK infusion; a significant reduction in mortality rate was observed in patients treated 12 hours or less after symptom onset (595). The high-dose GIK regimen is being tested in large, ongoing international trials. The potential beneficial effect of GIK in high-risk patients with acute ischemic syndromes who have been revascularized is supported by a study of 322 post–cardiac surgery patients with postoperative cardiogenic shock (598). Those assigned to GIK had a 34% (p less than 0.02) reduction in in-hospital mortality. GIK was not superior to placebo in a study of 940 patients who underwent primary PCI (597). There appeared to be an interaction between treatment and Killip class, with possible mortality reduction at 30 days in Killip class I patients and excess mortality for those in Killip class II or higher. No definitive recommendations regarding GIK can be formulated until ongoing trials are completed.

6.3.1.6.9.2.1. 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)***

The acute phase of STEMI is associated with a dramatic increase in catecholamine levels in the blood and ischemic myocardium. The insulin level remains low while cortisol and glucagon levels increase, which leads to decreased insulin sensitivity that contributes to impaired glucose utilization. Free fatty acid levels and the concentration of their metabolites increase, potentiating ischemic injury through several mechanisms: direct myocardial toxicity, increased oxygen demand, and direct inhibition of glucose oxidation. It has been suggested that agents that support glucose oxidation could reduce postischemic contractile dysfunction. Insulin promotes glucose oxidation, increases adenosine triphosphate levels, and may improve the fibrinolytic profile of patients with STEMI (599,600). Insulin reduces free fatty acids by reducing lipolysis and enhances glycolysis. Insulin specifically enhances glucose, lactate, and pyruvate uptake and switches the reliance of the myocardium from fat to carbohydrate without a change in oxygen consumption. The oxygen requirement of the heart is stimulated by free fatty acids without an improvement in mechanical activity (601).

Intensive insulin management of endogenous elevation of glucose in diabetics, supplemented by potassium as needed, has potential metabolic benefits similar to GIK for nondiabetics. The DIGAMI study randomized 620 diabetic patients to intensive insulin therapy with an insulin-glucose infusion for 24 hours followed by 3 months of subcutaneous injections of insulin 4 times daily or usual care (602). With continuous insulin infusion, blood glucose decreased in the first 24 hours from 15.4 to 9.6 mmol/L in the infusion group versus 15.7 to 11.7 mmol/L in the control group (p less than 0.0001). There was a trend toward lower 30-day mortality and significantly lower 1-year mortality (18.6% versus 26.1%, p equals 0.027).

Compelling evidence for tight glucose control in intensive care unit patients (a large proportion of whom were there after cardiac surgery) supports the importance of intensive insulin therapy to achieve a normal blood glucose (80 to 110 mg/dL) in critically ill patients (603,603a). Van den Berghe et al. reported that 12-month mortality rates were reduced from 8.0% to 4.6% (p less than 0.04; n equals 1548) for critically ill patients assigned to intensive insulin therapy (604). Goldberg et al. reported successful implementation of a nursing protocol with an insulin infusion to achieve a target blood glucose of 100 to 139 mg/dL in an intensive care setting (605). The studies by Van den Berghe et al. and Goldberg et al. underscore the importance and feasibility of intensive infusion therapy in the intensive care setting. The precise target blood glucose range requires further study.

Management of diabetic patients with STEMI should also involve consideration of long-term hypoglycemic therapy. A review of the oral hypoglycemic therapy of type 2 diabetes mellitus indicated that with few exceptions, the available oral antidiabetic agents are equally effective in lowering glucose levels. Their mechanisms of action are different. As a result, they appear to have distinct metabolic effects that may influence their profile and affect cardiovascular risk (606). As suggested by Inuzzuchi, in terms of hypoglycemic effect alone, there is no compelling reason to favor one of the major

Table 21. Trials of Glucose-Insulin-Potassium (GIK) for ST-Elevation Myocardial Infarction

Author (Reference)	Year	Sample Size	Hours From Onset of Symptoms to Starting GIK	Reperfusion Therapy	Mortality: GIK Dose	GIK vs Placebo	OR (95%CI)*	Follow-Up
Fath-Ordoubadi (meta-analysis) (594)	1997	1932	12-48	0.6% (100% Fibrinolytics)	4 Trials with high-dose GIK; 5 trials with low-dose GIK	16% vs 21%	0.72 (0.57-0.90) 0.58 (0.30-1.10)	Inhospital (3-4 wk)
Diaz (ECLA pilot) (595)	1998	407	Less than 24	62% (95% Fibrinolytics)	135 Patients with high-dose GIK; 133 patients with low-dose GIK	6.7% vs 11.5%	0.34† (0.78-10.1); 0.43‡ (0.2-0.9)	Inhospital (average 10.1 days)
Ceremuzynski (596)	1999	954	Less than 24	59% (100% Fibrinolytics)	Low-dose GIK	8.9% vs 4.5%	1.45 (0.79-2.68)	35 days
Zijlstra (597)	2003	940	N/A	100% (100% Primary angioplasty)	High-dose GIK	4.8% vs 5.8%	0.82	30 days

GIK = glucose-insulin-potassium; OR = odds ratio; CI = confidence interval; N/A = data not available.
*GIK compared with control.
†Fibrinolytic-treated patients.
‡GIK less than 12 hours.

classes of oral antidiabetic agents (606). The overarching principle is that diabetic patients with STEMI should ultimately receive a regimen that achieves the best glycemic control, is well tolerated, and is likely to be maintained by the patient over the long term.

Although it is well appreciated that type I diabetic patients require insulin, most type 2 diabetics will also eventually need insulin to achieve the target of a HbA1C level less than 7%, a value that has been shown to be associated with reduced cardiovascular complications. It is reasonable that the prescription for care of diabetics with STEMI be individualized, selected from an armamentarium of insulin, insulin analogs, and oral hypoglycemic agents alone or in combination (607). A popular combination is metformin with insulin because it results in similar metabolic control, less weight gain, lower insulin doses, and fewer hyperglycemic episodes than insulin alone or insulin plus sulfonylurea therapy (607). The use of metformin must be tempered with the knowledge that metformin is contraindicated in the presence of CHF and renal failure. It should be withheld for 48 hours after intravenous contrast injection (608).

6.3.1.6.9.3. 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 VT associated with a prolonged QT interval be treated with 1 to 2 grams of magnesium administered as an IV 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)*

Meta-analyses of 7 randomized trials published between 1984 and 1991 suggested a significant mortality benefit of magnesium (4.4% absolute risk difference [ARD]; OR 0.44, CI 0.27 to 0.71) (609,610). The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) subsequently reported a significant reduction in mortality with magnesium treatment (2.5% ARD; 24% RRR; p equals 0.03) (611).

The ISIS-4 investigators enrolled 58 050 patients, of whom 29 011 were allocated to magnesium and 29 039 to control (152). There were 2216 deaths (7.64%) by 35 days in the magnesium group and 2103 deaths (7.24%) in the control group (OR 1.06; CI 0.99 to 1.13), which suggests no mortality benefit of magnesium administration and even the possibility of slight harm. Critiques of ISIS-4 raised the possibility that the null effect of magnesium resulted from late administration of treatment to patients who were predominantly at low risk (612,613).

The MAGIC (Magnesium in Coronaries) trial investigated the benefits of early administration of intravenous magnesium to high-risk patients with STEMI (stratum I: age 65 years or older and eligible for reperfusion therapy; stratum II: patients of any age who were not eligible for reperfusion therapy) (614). At 30 days, 475 (15.3%) patients in the magnesium group and 472 (15.2%) in the placebo group had died (OR 1.0, 95% CI 0.9 to 1.2, p equals 0.96). Potential explanations for the null effect of magnesium in MAGIC include the possibility that publication bias and an inadequate sample size in several earlier trials could have led to an overestimation of the benefit of magnesium through a large type I error and that the combination of mechanisms proposed for the benefits of magnesium overlapped with and were superseded by aspirin, beta-blockers, and ACE inhibitors (prescribed infrequently in earlier trials but commonly in ISIS-4 and MAGIC).

Between 1980 and 2002, a total of 68 684 patients were studied in a series of 15 randomized trials (Table 22) (614-628). On the basis of the totality of available evidence, in current coronary care practice, there is no indication for the routine administration of intravenous magnesium to patients with STEMI at any level of risk. Magnesium can continue to be administered for repletion of documented electrolyte deficits and life-threatening ventricular arrhythmias such as torsade de pointes (629).

6.3.1.6.9.4. 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 ventricular response with AF or atrial flutter after STEMI in the absence of CHF, LV dysfunction, or 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 the treatment of STEMI because of the reflex sympathetic activation, tachycardia, and hypotension associated with its use. *(Level of Evidence: B)***

Nifedipine. In patients with STEMI, immediate-release nifedipine does not reduce the incidence of reinfarction or mortality when given early (less than 24 hours) or late. Immediate-release nifedipine may be particularly detrimental in patients with hypotension or tachycardia; in these patients, it may induce a reduction in coronary perfusion pressure, disproportionate dilatation of the coronary arteries adjacent to the ischemic area (so-called “steal”), and/or reflex activation of the sympathetic nervous system, with an increase in myocardial oxygen demands (630-637).

Table 22. Randomized Controlled Trials of Mg^{2+} in Myocardial Infarction

First Author, Year (Reference)	Start of Trial Treatment	Total Mg^{2+} Dose	Duration of Treatment, h	Early Mortality*		
				Control	Mg^{2+}	P Value
Morton, 1984 (615)	Less than 8 h after pain	90 mmol/80 kg	36	2/36	1/40	NS
Rasmussen, 1986 (616)	Less than 3 h after admission	62 mmol	48	23/135	9/135	Less than 0.01
Smith, 1986 (LIMIT-1) (617,618)	Less than 1 h after admission	65 mmol	24	23/185	15/180	NS
					1/48	NS
Abraham, 1987 (619)	Soon after admission	30 mmol	48	1/46	1/25	NS
Ceremuzynski, 1989 (620)	Less than 12 h after pain	32 mmol	24	3/23	1/59	Less than 0.01
Shechter, 1990 (621)	Soon after admission	88 mmol	48	9/56	10/150	NS
Feldstedt, 1991 (622)	Less than 8 h after pain	80 mmol	24	8/148	90/1135	Less than 0.05
Woods, 1992 (LIMIT-2) (623)	Median time less than 3 h	72 mmol	24	119/1129	18/130	NS
					4/96	Less than 0.01
Thogersen, 1993 (624)	Less than 1 h after admission	50 mmol	20	20/122	2216/29 011	NS
Shechter, 1995 (625)	Mean time 7 h after pain	92 mmol	48	17/98	6/169	Less than 0.01
ISIS-4, 1995 (255)	Median time less than or equal to 3 hours after fibrinolytic†	80 mmol	24	2103/29 039	2/50	Less than 0.05
Raghu, 1999 (626)	Less than 7 h after pain	76 mmol	24	18/181	475/3110	NS
Gyamlani, 2000 (627)	Less than 6 h after pain; less than 2 h after admission	62 mmol	48	10/50		
MAGIC, 2002 (614)	Median 3.8 h	77 mmol	24	472/3098		

h = hours; NS = not significant.
*Variously defined less than or equal to 35 days.
†Median 12 hours from onset in those not given fibrinolytic (30%).
Modified with permission from Woods and Abrams. Progress in Cardiovascular Diseases 2002;44:267-74 (628).

Verapamil. Although the overall results of trials with verapamil showed no mortality benefits, subgroup analysis showed that immediate-release verapamil initiated several days after STEMI in patients who were not candidates for a beta-blocking agent may have been useful in reducing the incidence of the composite end point of reinfarction and death, provided LV function was well preserved with no clinical evidence of heart failure. Verapamil is detrimental to patients with heart failure or bradyarrhythmias during the first 24 to 48 hours after STEMI (638-641). One randomized study of 1700 patients less than 75 years of age using verapamil within 2 weeks of STEMI showed a significant reduction in major events (death or reinfarction) over 18 months (3.6% ARD; 17% RRR; p equals 0.03) (642).

Diltiazem. Data from the Multicenter Diltiazem Postinfarction Trial (MDPIT; Q-wave and non–Q-wave infarction) (643) and the Diltiazem Reinfarction Study (DRS; non–Q-wave infarction) (639,640,644,645) suggest that patients with non–Q-wave MI or those with Q-wave infarction, preserved LV function, and no evidence of heart failure may benefit from immediate-release diltiazem. Diltiazem was begun in MDPIT 3 to 15 days after STEMI and in DRS 24 to 72 hours afterward. The results of MDPIT may be confounded by the fact that 53% and 55% of placebo- and diltiazem-treated patients, respectively, received concomitant beta-blocker therapy (643). Also, both the MDPIT and DRS projects were conducted in an era when the use of aspirin was not as prevalent as it is today, which raises further uncertainty about the relevance of their findings for contemporary management of STEMI. Of particular clinical importance is the detrimental mortality effect of diltiazem in patients with LV dysfunction.

Diltiazem was tested in patients with STEMI but without CHF who were undergoing fibrinolytic therapy in the INTERCEPT trial (Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis) (646). No effect on the cumulative occurrence of fatal and nonfatal end points was demonstrated during a 6-month follow-up, but there was a modest decrease in nonfatal cardiac events, in large part due to reductions in recurrent ischemia.

7. HOSPITAL MANAGEMENT

7.1. Location

7.1.1. 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 coronary 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)*

Treatment of the patient with STEMI begins in the EMS system/ED/catheterization laboratory and is consolidated in the CCU. On arrival at the CCU, initial patient evaluation includes assessment of vital signs, pulse oximetry, cardiac rhythm and ST segments, and symptoms of acute cardiac ischemia. Research has also shown the importance of assessing anxiety and depression, because outcomes are worse in patients with even moderate elevations in dysphoria. Outstanding (and abnormal) laboratory results should be followed up, and standard orders to CCU should be implemented. All CCUs should have the equipment and personnel necessary to monitor intra-arterial pressure and pulmonary artery catheter pressures (Swan-Ganz catheter). Such monitoring is useful for severely hypotensive patients. An IABP should be available in tertiary care CCUs for treatment of cardiogenic shock. The patient's medication orders 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 acute heart failure.

Ideally, all CCU nursing staff should have certification in critical care nursing (CCRN, Critical Care Registered Nurse) as endorsed by the American Association of Critical-Care Nurses (647). Advanced cardiac life support certification (ACLS) is highly recommended. The need for ACLS certification is usually determined by institutional policy.

There has been documentation of the positive correlation between nurse staffing levels and patient outcome in intensive care units (648-650). The nurse-to-patient ratio has varied depending on nurse availability and the needs of the

patient, e.g., 1 nurse per patient for an intubated patient, to 1:2 (651). In 1999, the state of California mandated a ratio of 1:2 in the intensive care unit/CCU, 1:4 in the stepdown unit, and 1:5 in the telemetry unit (652). A study of the effect of the California state law showed a continued wide variation of staffing ratios among hospitals (653). The American Association of Critical Care Nurses has issued a policy statement that staffing decisions in the critical care setting should optimally be based on the specific needs of patients and provider competencies, as well as organizational priorities. Within this framework, staffing should reflect the number and type of staff that meet a group of patients' needs instead of a mandated single staffing ratio or mix (654).

Patients with STEMI may experience heart failure, serious arrhythmias, or recurrent ischemia (655). Accordingly, nursing-related care is commonly prescribed as part of a standing order (i.e., measurement of height and weight on admission and thereafter daily weight, especially if heart failure is present; routine post-STEMI vital signs, including oxygen saturation; ECG monitoring; and activity level such as bathroom privileges and progressive cardiac rehabilitation). Medications such as stool softeners or antianxiety agents should be given based on nursing judgment.

The current medical-legal-economic climate demands that CCUs be operated at peak efficiency, optimizing quality of care and minimizing complications. Practical and ethical dilemmas present the CCU director with issues of futile care, triage, and the administration of appropriate care (656). It is generally accepted that terminal patients (no-code) or patients whose comorbidities make survival unlikely should not be admitted to a CCU. Similarly, patients with improving CHF or stable dysrhythmia should be transferred to a non-CCU, monitored bed.

7.1.1.1. Monitoring and Treatment for Adverse Events

Early general measures focus on monitoring for adverse events, preventing such events through protective measures, and treating these adverse events when they do occur. Electrocardiographic monitoring is an essential role of CCU staff, who must be adept at rhythm interpretation, lead selection based on infarct location and rhythm, and lead placement for detection of RV involvement (657-660). Computer algorithms have proved superior to medical personnel for detection of arrhythmias (661). Accurate and consistent lead placement and careful electrode and skin preparation are important to improve the clinical usefulness of ST monitoring (662).

Nurses should monitor the ST segment for ischemia, particularly during routine morning care, because patients have been reported to have a greater likelihood of ischemic events between 6 AM and noon than at other times (663). Currently, ECG monitors operate with computerized arrhythmia analysis alone or with both arrhythmia and ischemia analysis. ST-segment monitoring is generally underutilized in American hospitals.

Because changes in the ST segment can shift among various ECG leads in the same person over time owing to different ischemic mechanisms, a consensus statement on ST monitoring has recommended that 12-lead monitoring be done (662). Patients with acute coronary syndromes, including STEMI, are the highest priority for ST-segment monitoring. It is recommended they be monitored for a minimum of 24 hours and until they remain event-free for 12 to 24 hours. Potential benefits in patients with STEMI include the ability to assess patency of the culprit artery after fibrinolytic therapy (664-668); detect abrupt reocclusion after PCI (669); detect ongoing ischemia (i.e., failed reperfusion therapy), recurrent ischemia, and infarct extension; and detect transient myocardial ischemia.

Blood pressure should be measured repeatedly; actual frequency will depend on the severity of the illness. Although invasive arterial monitoring is preferred in the hypotensive patient, noninvasive monitoring is adequate for most patients. Monitoring with an automatic device that inflates and deflates at programmed intervals is useful, but it must be recognized that measurements may be inaccurate because of inappropriate cuff size or muscle contractions; marked peripheral vasoconstriction can result in falsely low readings. Furthermore, many patients report that the device is irritating and disrupts rest.

7.1.2. 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., AF 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/continuous positive airway pressure 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)***

Although the CCU was traditionally the hospital location to which patients with STEMI were first admitted, increasing use of catheter-based reperfusion and increasing sophistication of monitoring equipment and staff experience has resulted in a shift toward admitting patients with low-risk STEMI who have undergone successful reperfusion with PCI directly to a stepdown unit. In addition, patients originally admitted to the CCU who demonstrate 12 to 24 hours of clinical stability are typically transferred to the stepdown unit. The same nurse staffing and certification considerations apply to the stepdown unit (coronary observation unit, telemetry unit) as described for the CCU to ensure optimal evaluation and response to any deterioration of the patient with STEMI. Pulse oximetry and ECG monitoring and defibrillation equipment should be available. Optimally, the nursing staff should have a skill set similar to CCU nurses so that they may evaluate and respond to any deterioration of a patient with STEMI. The initial evaluation of patients with STEMI who are admitted directly to the stepdown unit is similar to that described in Section 7.1.1 for the CCU.

7.2. Early, General Measures

7.2.1. 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)***

Limiting early physical exertion and minimizing sympathetic stimulation (e.g., acute ischemic-type chest discomfort and anxiety) are methods of minimizing myocardial oxygen demand (670). In an earlier era, the duration of bed rest was extended to several weeks, until it was ascertained that prolonged immobility is harmful because of the physiological deconditioning that occurs after even 6 hours in the supine position (671). Preload decreases because of plasma volume losses that occur early in the bedrest period. Shifts in ventricular filling activate the body's compensatory mechanisms to buffer pressure and volume alterations.

The current literature suggests that the deconditioning effects of bedrest are independent of the patient's clinical condition but rather are associated with the absence of regular exposure to "orthostatic stress" (produced by assumption of an upright posture). The absence of habitual exposure to the upright posture occurs naturally with prolonged periods of bedrest and deprives the cardiovascular system of stimulation needed to maintain adequate blood pressure regulation. As a result, these patients commonly develop orthostatic hypotension or frank syncope during their initial ambulation attempt in the in-patient setting. Studies have found that intermittent but regular exposure to sitting or standing during convalescence can counteract these deconditioning effects (672).

The 1996 ACC/AHA Guidelines for the Management of Patients with Acute MI cited evidence of the continued practice of "coronary precautions" that were advocated in the 1960s (2), and specific directions were given about what were or were no longer considered to be coronary precautions. It is assumed that current practice has advanced sufficiently such that patients with STEMI are no longer kept on bedrest or fed by nurses. Avoidance of the Valsalva maneuver remains an important consideration (673,674), especially in younger patients (e.g., under the age of 45 years) (673-676). Otherwise, current practice routinely entails a short period of bedrest (except for patients who have recurrent ischemic discomfort, symptoms of heart failure, or serious rhythm disturbances). Low-level activities such as toileting, assisted bathing, and light ambulation can prevent physiological deconditioning (673-676). Sample admitting orders reflecting the standard of care are presented in Table 23 (3).

7.2.2. 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)***

The NCEP ATP III has recommended that a complete blood lipid profile be taken in all patients with established CHD (50). In the STEMI patient, this should be done at the time of admission or within 24 hours of the onset of symptoms, because low-density lipoprotein cholesterol (LDL-C) levels begin to decrease soon after an event and are significantly reduced by 48 hours and remain so for many weeks. Thus, LDL-C measurements several days after STEMI may

Table 23. Sample Admitting Orders for the Patient With STEMI

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 h until stable, then every 4 h 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 diastolic, respiratory rate is less than 8 or greater than 22 bpm.
4. **Monitor**: Continuous ECG monitoring for arrhythmia and ST-segment deviation.
5. **Diet**: NPO except for sips of water until stable. Then start 2 grams sodium/day, low saturated fat (less than 7% of total calories/day), low cholesterol (less than 200 mg/d) 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 L/min when stable for 6 h, reassess for oxygen need (i.e., O_2 saturation less than 90%), and consider discontinuing oxygen.
8. **Medications**:
   a. **Nitroglycerin** (See Section 6.3.1.2 for further discussion.)
      1. Use sublingual NTG 0.4 mg every 5 min as needed for chest discomfort.
      2. Intravenous NTG for CHF, hypertension, or persistent ischemia.
   b. **Aspirin** (See Section 6.3.1.4.)
      1. If aspirin not given in the ED, chew non–enteric-coated aspirin† 162 to 325 mg.
      2. If aspirin has been given, start daily maintenance of 75 to 162 mg. May use enteric-coated for gastrointestinal protection.
   c. **Beta-Blocker** (See Section 6.3.1.5.)
      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 HR and BP.
   d. **ACE Inhibitor** (See Section 6.3.1.6.9.1.)
      1. Start ACE inhibitor orally in patients with anterior infarction, pulmonary congestion, or LVEF less than 0.40 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** (See Section 6.3.1.6.9.1.)
      1. Start ARB orally in patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF less than 0.40.
   f. **Pain Medications** (See Section 6.3.1.3.)
      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) (See Section 7.2.4.)
   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).

STEMI = ST-elevation myocardial infarction; IV = intravenous; NS = normal saline; h = hours; bpm = beats per minute; ECG = electrocardiogram; NPO = nothing by mouth; min = minutes; NTG = nitroglycerin; CHF = congestive heart failure; ED = emergency department; HR = heart rate; BP = blood pressure; ACE = angiotensin converting enzyme; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; ARB = angiotensin receptor blocker; CBC = complete blood count; INR = international normalized ratio; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen.

*Do not wait for results before implementing reperfusion strategy.

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

Modified with permission from Ryan et al. J Am Coll Cardiol 1999;34:890-911 (3).

not be representative of the patient's average LDL-C. In the context of possible early cardiac catheterization, it would be helpful for patients to have been on a clear liquid diet that extended to a period of "nothing by mouth" (NPO) before the procedure. Patients with STEMI should receive a reduced saturated fat and cholesterol diet per the ATP III TLC approach (677). (See Section 7.12.2.) Diabetes experts no longer recommend a single meal plan for all people with diabetes. Instead, they recommend meal plans that are flexible and take into account a person's lifestyle and particular health needs, ideally with consultation from a registered dietitian to design a meal plan. Sodium intake should be restricted in patients with STEMI with hypertension or heart failure to a maximum of 2000 mg/d (Table 23) (3).

Blood pressure increases after caffeine intake (678), but the increase is not clinically significant until 400 mg of caffeine (i.e., 2 to 4 cups of coffee, depending on strength and brewing method) is ingested (679,680). Moderately high doses (450 mg) of caffeine did not increase ventricular arrhythmias in a small group of patients with ischemic heart disease (681). People who drink caffeinated beverages regularly develop a tolerance after 1 to 4 days (682,683), regardless of dose. Withdrawal of caffeine is associated with headache (684,685) and increases in heart rate (686). The available evidence suggests that patients with STEMI who are routine caffeine drinkers be allowed to consume up to 4 to 5 cups of caffeinated coffee a day while in the CCU or progressive care unit, under the surveillance of nursing staff (680,687). As a practical matter in the acute care setting, 1 to 2 cups of coffee, enough to avert caffeine withdrawal, seems appropriate.

7.2.3. 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's "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)***

Patient education should be viewed as a continuous process that should be part of every patient encounter (i.e., on hospital arrival, at inpatient admission, at discharge, and at follow-up visits). On admission to the coronary care unit, patients should receive an orientation to their surroundings (e.g., location of the call light), an explanation of the equipment used for their care (e.g., electrodes and cardiac monitor, IV line/heparin lock, central line, nasal cannula, and pulse oximetry), nursing care routines and their "round-the-clock" nature, level of activity permitted, an explanation of the pain assessment scale that will be used, and the importance of reporting any symptoms.

In general, effective education involves the use of a combination of good communication skills, patient assessment of prior knowledge and readiness to learn, and effective teaching strategies. One-to-one teaching is the most common patient education method in the inpatient setting and is preferred by patients as well (688). Ideally, family members should be present to hear what patients are being told so they can reinforce the information later (689).

For more complex topics, the most effective educational intervention involves being responsive to the patient's attempts to communicate (e.g., not changing the topic abruptly or engaging in tasks unrelated to the conversation); using good eye contact; not denying the patient's feelings (e.g., "You should not worry about that!"); and being aware of one's own nonverbal cues that encourage or discourage communication (e.g., failure to sit down), as well as those of the patient's.

Inpatient education has been reported to stimulate some lifestyle change after discharge, most frequently in the areas of activity and smoking cessation (690). However, post-MI knowledge alone does not ensure behavioral change (691,692). Providers should be aware that many patients who have had a STEMI may be in the early stages of behavioral change, such as "precontemplation," where they do not yet see a need to change behavior. Others may be in the "contemplation" stage, where, for example, the experience of STEMI may cause them to acknowledge that they need and want to make a change, but that thought is not yet translated into action (691-694).

With 1-to-1 teaching in the hospital, the provider should strike a balance between not using any teaching aids when educating the patient and simply handing out written information or other media without discussion. One-to-one teaching is effectively enhanced and reinforced with the use of appropriate media (688,695).

Challenges to patient education in the inpatient setting are shorter lengths of hospital stay (696); older, sicker patients with more psychosocial issues; cultural and literacy barriers (697); and patient anxiety (698). Inpatient education has been shown to reduce anxiety (699,700), improve knowledge (688), and decrease length of hospital stay (700,701).

In standardizing care for these patients, the use of guideline-based tools has been reported to facilitate improvement in the quality of care for patients with STEMI among a variety of institutions, patients, and caregivers (5). Programs such as the AHA's "Get With the Guidelines" (see the "Get With the Guidelines' Hospital Tool Kit" at: http://www.americanheart.org/downloadable/heart/1107_HospTool.pdf) and the ACC's "Guidelines Applied in Practice" (see sample forms at: http://www.acc.org/gap/mi/ami_permissionprocess.htm) offer tools such as educational plans for patients explaining what they can expect over the course of their hospitalization (e.g., procedures and the treatment plan), care paths, standing orders for providers, discharge protocols that incorporate evidence-based recommendations (for providers and patients), and a data-based patient management tool (702).

Support groups provided by some hospitals and cardiac rehabilitation programs may help patients adjust to their diagnosis and newly prescribed lifestyle and medication regimens. For example, Mended Hearts is a national nonprofit organization affiliated with the AHA that offers visiting programs, support group meetings, and educational forums through partnerships with hospitals and rehabilitation clinics. The organization is particularly interested in helping patients deal with the emotional recovery from heart disease through facilitating a positive patient-care experience for heart disease patients, their families, caregivers, and others impacted by heart disease (703). Table 24 shows suggested topics for educating the patient with STEMI.

7.2.4. 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)***

It is useful to monitor patients for increased anxiety or altered behavior of the patient in the CCU. Anxiolytics can play an important role in patient management in this setting. Treatment with benzodiazepines should be limited to the minimal dose for a limited period of time (261).

Hospitalized smokers may experience symptoms of nicotine withdrawal, including anxiety, insomnia, depression,

Table 24. Milestones and Recommended Information for Educating the Patient With ST-Elevation Myocardial Infarction

Following is the range of information providers should address with patients with STEMI and their family members:

Before the event—(ongoing by primary care provider, especially with high-risk patients)
- Assess and manage cardiac risk factors
- Review recommendations for recognizing and responding to heart attack symptoms (See: http://www.nhlbi.nih.gov/health/prof/heart/mi/provider.htm)

At hospital/ED admission—(day of admission)
- Explain diagnosis
- Review plan for inpatient treatment and projected length of stay

Inpatient testing/procedures—(day of admission until discharge)
- Explain the purpose of tests and procedures that are ordered
- Describe what to expect with tests and procedures: duration; level of discomfort and invasiveness; sensory information

Cardiac care unit/stepdown unit—(day of admission)
- Orient to surroundings/routine of unit
- Explain nursing care plan
- Describe the importance of reporting symptoms, needs

At discharge—(day of discharge or before)
- Review risk factor goals and management plan
- Review prescribed medications and lifestyle changes/recommendations
- Review information on recognizing and responding to heart attack symptoms
- Recommend that family member(s) attend a CPR training program and cardiac support group
- Refer patient to cardiac rehabilitation program
- Schedule a follow-up appointment with primary care provider
- Discuss plans for obtaining prescribed medication that day (immediately after discharge)

At follow-up visits with primary care provider—(first follow-up appointment and ongoing)
- Review diagnosis with patient and hospital course/outcome
- Review medical and lifestyle regimens prescribed
- Ensure aggressive risk factor modification and follow-up
- Discuss recognition and response to acute symptoms; review action plan, including taking nitroglycerin in response to acute symptoms if prescribed, and calling 9-1-1
- Assess for depression, other psychosocial responses

Suggested milestones for educating patients over the spectrum of cardiac care, both before and after the STEMI event. Risk factor assessment and management and counseling about recognition and response to heart attack symptoms should be done by the primary care provider. Once admitted for STEMI, the provider should review with the patient and family members the diagnosis, treatment plan, and projected length of stay; purpose and what to expect of tests and procedures that are ordered; the coronary care unit (or equivalent) environment and nursing care plan; and at discharge, the prescribed medications and lifestyle changes, follow-up testing, and referral.

STEMI = ST-elevation myocardial infarction; ED = emergency department; CPR = cardiopulmonary resuscitation.

difficulty concentrating, irritability, anger, restlessness, and slowed heart rate (704). Patients experiencing nicotine withdrawal can benefit from anxiolytics. Use of bupropion and nicotine replacement therapy in the acute setting should also be considered as options, depending on the severity of the patient's withdrawal syndrome. Agitation and delirium are not uncommon in the CCU, particularly in patients with complicated STEMI and protracted stays in the intensive care setting. In addition, a number of medications used in the CCU, such as lidocaine, mexiletine, procainamide, atropine, cimetidine, and meperidine, can induce delirium. Intravenous haloperidol is a rapidly acting neuroleptic that can be given safely and effectively to cardiac patients with agitation. It rarely produces hypotension or need for assisted ventilation. If patients exhibit altered sensorium and have received fibrinolytics, consideration should be given to ordering a computed axial tomography/magnetic resonance imaging scan to rule out ICH before sedating the patient.

Anxiety and depression are prevalent in patients hospitalized for STEMI because patients are confronted with a diagnosis that is major, both psychologically and physically (705,706). In addition, the experience of a cardiac event is a significant source of stress for family members trying to adjust to the initial diagnosis and confront the uncertainties associated with hospitalization and the initial recovery phase. Anxiety has been demonstrated to predict inhospital recurrent ischemia and arrhythmias (707) and cardiac events during the first year after an MI (708). Physicians' and nurses' subjective judgments of patient anxiety are not accurate when compared with measurements of anxiety on validated scales (709,710).

The provision of information, discussed later in this guideline, and liberal visiting policies can also help patients with STEMI feel more in control (711,712). In addition, psychological support and counseling during hospitalization can decrease anxiety and depression immediately and for up to 6 months after STEMI (713,714). At least 1 randomized controlled trial demonstrated that in-hospital anxiety and depression could be reduced by a structured nursing support intervention (714).

Liberalized visiting rules for patients in critical care can be helpful; several studies have demonstrated no harmful phys-

iological effects attributable to unrestricted visiting policies (711,712). Patients whose anxiety is very severe or persistent in spite of medications should be referred for consultation for formal anxiety assessment and treatment. Consultation could be obtained from a nurse specialist, psychiatric social worker, or a psychiatrist.

7.3. Risk Stratification During Early Hospital Course

Several groups have proposed risk stratification scores for patients with suspected STEMI based on their admission characteristics (241,242,394). Risk stratification is a continuous process and requires the updating of initial assessments with data obtained during the hospital stay. Indicators of failed reperfusion (e.g., recurrence of chest pain, persistence of ECG findings indicating infarction) identify a patient who should undergo coronary angiography. Similarly, findings consistent with mechanical complications (e.g., sudden onset of heart failure, presence of a new murmur) herald increased risk and suggest the need for rapid intervention. For patients who did not undergo primary reperfusion, changes in clinical status (e.g., development of shock) may herald a worsening clinical status and are an indication for coronary angiography.

Patients with a low risk of complications may be candidates for early discharge. The lowest-risk patients are those who did not have STEMI, despite the initial suspicions. Clinicians should strive to identify such patients within 8 to 12 hours of onset of symptoms. Serial sampling of serum cardiac biomarkers and use of 12-lead ECGs and their interpretation in the context of the number of hours that have elapsed since onset of the patient's symptoms can determine the presence of STEMI better than adherence to a rigid protocol that requires that a specified number of samples be drawn in the hospital. Among those with STEMI treated with reperfusion, it has been suggested that an uncomplicated course after 72 hours of hospitalization identifies a group with a low enough risk for discharge (715). Newby and colleagues calculated that extending the hospital stay of these patients by another day would cost $105 629 per year of life saved (715). Concerns have been raised that shortening the length of stay to 72 hours may adversely affect patient education regarding STEMI and the identification of the optimum dose of critical medications such as beta-blockers and ACE inhibitors (696). Work on transitional care has shown the effectiveness of an advanced practice nurse intervention in helping patients, many with ischemic heart disease, during the transition from hospital to home and in reducing costs in the process (716).

7.4. Medication Assessment

7.4.1. 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 re-evaluated for candidacy for beta-blocker therapy.** ***(Level of Evidence: C)***

There is overwhelming evidence for the benefits of early beta-blockade in patients with STEMI and without contraindications to their use (see Section 6.3.1.5). Benefits have been demonstrated for patients with and without concomitant fibrinolytic therapy, both early and late after STEMI. Meta-analysis of trials from the prefibrinolytic era involving more

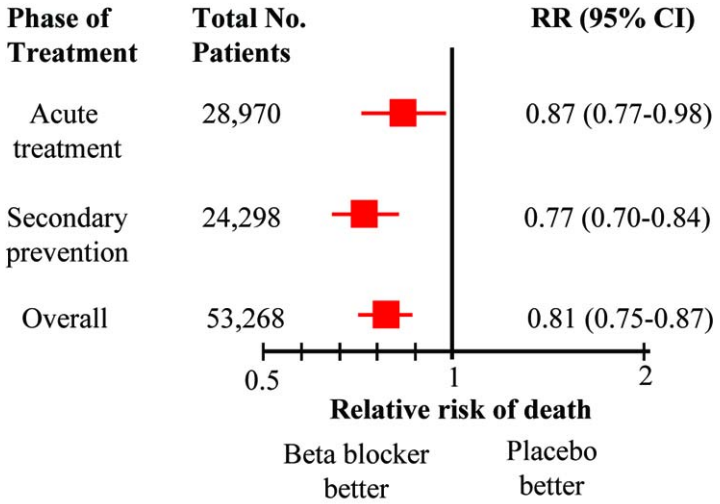


Figure 27. Summary of data from meta-analysis of trials of beta-blocker therapy from the prefibrinolytic era in patients with myocardial infarction. No. = number; RR = relative risk; CI = confidence interval. Reprinted with permission from Antman and Braunwald. Acute Myocardial Infarction. In: Braunwald, Zipes, Libby, eds. Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Philadelphia, PA: W.B. Saunders; 2001:1168 (718).

than 24 000 patients receiving beta-blockers in the convalescent phase showed a 14% RRR in mortality through 7 days and a 23% RRR in long-term mortality (717). These data are summarized in Figure 27 (718).

Beta-blockers should be initiated early in the course of STEMI and continued unless adverse effects have been observed. In appropriately selected patients, these benefits occur at a risk of approximately a 3% incidence of provocation of CHF or complete heart block and a 2% incidence of the development of cardiogenic shock. Beta-blockers are especially beneficial in patients in whom STEMI is complicated by persistent or recurrent ischemia, evidence for infarct extension, or tachyarrhythmias.

Some clinicians do not start beta-blockers in the emergency phase of STEMI management because of error, late presentation, concern about relative or absolute contraindications, or concern about the benefits of beta-blockade in the face of other contemporary treatments. Benefits of beta-blockers initiated in the convalescent phase for secondary prevention of ischemic events are established (717). The Beta-blocker Heart Attack Trial (BHAT) (719) and the more contemporary CAPRICORN trial (273) confirm the substantial benefit of beta-blockers in addition to ACE inhibitor therapy in patients with transient or sustained postinfarction LV dysfunction. A reasonable general rule is to initiate beta-blockade after 24 to 48 hours of freedom from a relative contraindication, such as bradycardia, mild-to-moderate heart failure, or first-degree heart block.

7.4.2. 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 take into account that it 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 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 RV infarction. *(Level of Evidence: C)*

The use of nitrates in the patient with STEMI on presentation and in the early phase of infarction is reviewed in Section 6.3.1.2. Clinical trials have suggested only a modest benefit of nitroglycerin used acutely in STEMI and continued subsequently (152,586). Nitrates are most clearly indicated for persistent or recurrent ischemia and in patients with CHF. Because protocols in large clinical trials included acute followed by sustained therapy, there is little evidence to establish the duration of nitrate therapy after STEMI. Common clinical practice is to continue nitrate therapy for 24 to 48 hours. In view of their marginal treatment benefits, nitrates should not be used if hypotension limits the administration of beta-blockers or ACE inhibitors, which have more powerful benefits for both early use and secondary prevention after STEMI.

Nitrate tolerance develops with prolonged continuous exposure to nitrates, presumably through the mechanism of depletion of sulfhydryl groups in the vessel wall. If sustained therapy with nitrates is planned, intravenous nitrate therapy is usually changed to oral or topical preparations with a nitrate-free interval.

7.4.3. 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 of 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 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)*

The use of ACE inhibitors in the initial management of the patient with STEMI is reviewed in Section 6.3.1.6.9.1.

The proportional benefit of ACE inhibitor therapy is largest in higher-risk subgroups, including those with previous

infarction, heart failure, depressed LVEF, and tachycardia (585,589,720). Survival benefit for patients more than 75 years old and for a low-risk subgroup without the features noted above is equivocal (589,720).

The duration of ACE inhibitor therapy after STEMI requires detailed analysis of trial results. In general, the trials that administered ACE inhibitors to an unselected population of patients early after MI had a short follow-up of 5 to 7 weeks. In contrast, trials that selected patients with post-MI LV dysfunction or clinical heart failure followed patients up to 5 years. Thus, when there is no evidence of symptomatic or asymptomatic LV dysfunction by 4 to 6 weeks, the indications for long-term ACE inhibitor use should be re-evaluated. The Heart Outcomes Prevention Evaluation (HOPE) trial enrolled patients whose entry characteristics were age 55 years or older, evidence of vascular disease, or diabetes plus 1 other cardiovascular risk factor (721). In the HOPE population, the use of ramipril at doses up to 10 mg daily demonstrated a significant reduction in the primary outcome, a composite of MI, stroke, or death of cardiovascular causes (3.8% absolute risk reduction; RRR 0.78, 95% CI, 0.70 to 0.86; p less than 0.001).

Aldosterone blockade is another means of inhibiting the renin-angiotensin-aldosterone system that has been applied to patients in the post-STEMI setting. Again, additional information can be inferred from heart failure studies that enrolled a large proportion of patients with a history of MI. The RALES study (Randomized Aldactone Evaluation Study) randomized patients with New York Heart Association class III to IV heart failure to either spironolactone (initial dose 25 mg daily with the option to increase to 50 mg daily) or placebo (722). Ischemic heart disease was the cause of heart failure in 55% of patients, and 95% were treated concurrently with an ACE inhibitor. Over 24 months of follow-up, spironolactone treatment was associated with an 11% ARD (24% RRR) in all-cause mortality. The EPHESUS study (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) randomized 6632 post-MI patients with an ejection fraction of 0.40 or less and heart failure or diabetes to receive the aldosterone blocker eplerenone (target dose 50 mg daily) or placebo in conjunction with routine indicated cardiac medications. There was a significant reduction in overall mortality, cardiovascular mortality, and cardiac hospitalizations (723). The benefit was seen in patients managed with optimal therapy, including reperfusion, aspirin, ACE inhibitors, beta-blockers, and statins. Thus, the RALES and EPHESUS studies support the long-term use of an aldosterone blocker in patients with STEMI with heart failure and/or an ejection fraction of 0.40 or less, provided the serum creatinine is less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women and serum potassium concentration is less than or equal to 5.0 mEq/L. The risk of hyperkalemia was greatest in patients with creatinine clearance estimated to be less than 50 mL/min. Close monitoring of potassium levels is indicated for those patients, and the risk-to-benefit ratio should be weighed for those with moderate to severe reductions despite a serum creatinine of less than 2.5 mg/dL.

The use of ARBs after STEMI has not been explored as thoroughly as ACE inhibitors in patients with STEMI. The OPTIMAAL trial (Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan) found no significant differences between losartan (target dose 50 mg once daily) and captopril (target dose 50 mg 3 times daily) in all-cause mortality (724), but there was a trend toward better outcome with captopril. The VALIANT trial (Valsartan in Acute Myocardial Infarction Trial) compared the effects of captopril (target dose 50 mg 3 times daily), valsartan (target dose 160 mg twice daily), and their combination (captopril target dose 50 mg 3 times daily; valsartan target dose 80 mg twice daily) on mortality in post-MI patients with LV dysfunction (725). During a median follow-up of 24.7 months, death occurred in 19.9% of the valsartan group, 19.5% of the captopril group, and 19.3% of the combined-treatment group. The hazard ratio for death in the valsartan group compared with the captopril group was 1.00 (97.5% CI, 0.90 to 1.11; p equals 0.98), and the hazard ratio for death in the valsartan and captopril combined versus the captopril group was 0.98 (97.5% CI, 0.8 to 1.09; p equals 0.73) (725). The combination captopril and valsartan group had the most drug-related adverse events. In the monotherapy groups, hypotension and renal dysfunction were more common in the valsartan group, and cough, rash, and taste disturbance were more common in the captopril group.

Given the extensive randomized trial and routine clinical experience with ACE inhibitors, they remain the logical first agent for inhibition of the renin-angiotensin-aldosterone system in patients convalescing from STEMI (726). Valsartan monotherapy (target dose 160 mg twice daily) should be administered to patients with STEMI who are intolerant of ACE inhibitors and who have evidence of LV dysfunction. Valsartan monotherapy can be a useful alternative to ACE inhibitors; the decision in individual patients may be influenced by physician and patient preference, cost, and anticipated side-effect profile.

7.4.4. 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, the drug should be withheld for at least 5 days if possible, 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 sev-**

eral months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel) and for up to 12 months in patients who are not at high risk for bleeding. ***(Level of Evidence: B)***

Aspirin. The use of aspirin in patients with STEMI on initial presentation and in early management is discussed above (Sections 6.3.1.4 and 6.3.1.6.8.2.1). Aspirin should be given to the patient with suspected STEMI as early as possible and continued indefinitely, regardless of the strategy for reperfusion and regardless of whether additional antiplatelet agents are administered. True aspirin allergy is the only exception to this recommendation. Maintenance aspirin doses for secondary prevention of cardiovascular events in large trials have varied from 75 to 325 mg per day, but no trial has directly compared the efficacy of different doses after STEMI. An overview of trials with different doses of aspirin in the long-term treatment of patients with coronary disease suggests similar efficacy for daily doses ranging from 75 to 325 mg (727). An analysis from the CURE trial (Clopidogrel in Unstable angina to prevent Recurrent Events) suggests a dose-dependent increase in bleeding in patients receiving aspirin plus placebo: The major bleeding event rate was 2.0% in patients taking less than 100 mg of aspirin, 2.3% with 100 to 200 mg, and 4.0% with greater than 200 mg per day (728,729). Therefore, lower aspirin doses of 75 to 162 mg per day are preferred for long-term treatment.

The side effects of aspirin are mainly gastrointestinal and dose related (730). Gastric side effects may also be reduced by administration of diluted solutions of aspirin (731), treatment with H2 antagonists (732), antacids (731,733), or use of enteric-coated or buffered aspirin (734,735).

Aspirin should be avoided in those with a known hypersensitivity and used cautiously in those with blood dyscrasias or severe hepatic disease (see additional discussion in Sections 7.12.5 and 7.12.11). If the patient has a history of bleeding peptic ulcers, the use of rectal aspirin suppositories may be safer because it eliminates the local effect of aspirin on the gastric mucosa. However, antiplatelet effects may still pose a risk. Another potentially deleterious effect of aspirin is risk of bleeding from surgical sites. Patients who received aspirin in the Veterans Administration Cooperative Study (736) were noted to have significantly increased postoperative chest drainage and reoperation for bleeding (6.5% for aspirin groups compared with 1.7% for nonaspirin groups; p less than 0.01). Others have noted that preoperative aspirin use has been associated with increased postoperative chest drainage but not an increased rate of reoperation for bleeding (737,738). In another Veterans Administration Cooperative Study (739), starting aspirin 6 hours after surgery conferred the benefits of improved saphenous vein bypass graft patency without the increased postoperative bleeding seen with preoperative administration of aspirin. Aspirin (81 to 365 mg) should be administered as soon as possible (within 24 hours) after CABG unless contraindicated (see Section 7.10.7).

Use of the thienopyridines ticlopidine and clopidogrel in the early management of STEMI is discussed above (Section 6.3.1.6.8.2.2). Clopidogrel 75 mg daily is generally preferred to ticlopidine 250 mg twice daily because of fewer side effects and once-daily dosing (740,741).

In the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial of patients with UA/NSTEMI, there was a statistically significant risk reduction in vascular death, MI, or stroke in favor of clopidogrel (0.51% ARD; RRR 8.7%) (742). Clopidogrel has also demonstrated efficacy in addition to aspirin versus aspirin alone in patients with acute coronary syndrome (728). Therefore, a thienopyridine (preferably clopidogrel) should be substituted for aspirin in patients with STEMI for whom aspirin is contraindicated because of hypersensitivity or major gastrointestinal intolerance. On the basis of several randomized trials of combination antiplatelet therapy (577,741,743), clopidogrel, in combination with low-dose aspirin (75 to 162 mg, to minimize the risk of bleeding), is recommended for all patients after stent implantation (432).

7.4.5. Antithrombotics

Class I

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

Class IIa

It is reasonable that STEMI patients not undergoing reperfusion therapy who do not have a contraindication to anticoagulation be treated with intravenous or subcutaneous UFH or with subcutaneous LMWH for at least 48 hours. In patients whose clinical condition necessitates prolonged bedrest and/or minimized activities, it is reasonable that treatment be continued until the patient is ambulatory. ***(Level of Evidence: C)***

Class IIb

Prophylaxis for DVT with subcutaneous LMWH (dosed appropriately for specific agent) or with subcutaneous UFH, 7500 to 12 500 U twice per day until completely ambulatory, may be useful, but the effectiveness of such a strategy is not well established in the contemporary era of routine aspirin use and early mobilization. ***(Level of Evidence: C)***

In patients treated with fibrinolytic therapy, there is little evidence of the benefit of UFH in the modern era, during which aspirin, beta-blockers, nitrates, and ACE inhibitors are routinely available. Nevertheless, the best available data emanate from a series of randomized clinical trials performed before the reperfusion era. A systematic overview of these studies demonstrated a reduction in mortality (3.5% ARD; 23% RRR) and a reduction in risk of reinfarction (1.5% ARD; 18% RRR) with UFH (537). The control groups

in these trials were not treated with other therapies, particularly aspirin, that are now considered routine. Notwithstanding this, it is primarily these randomized data from an earlier era that support the recommendation to use UFH in patients not treated with fibrinolytic therapy.

The occurrence of a large anterior infarction, documentation of thrombus in the LV by echocardiography, history of a previous embolic event, and AF have been associated with a high risk of embolic stroke. Although no randomized trial evidence exists to demonstrate a definite benefit specific to this group, some empirical evidence exists that the risk of systemic emboli in the general population of MI patients can be reduced by early initiation of UFH (744). In the SCATI trial (Studio sulla Calciparina nell'Angina e nella Trombosi Ventricolare nell'Infarto), patients were randomly assigned to a 2000-IU bolus of UFH followed by 12 500 U subcutaneously twice per day or to placebo. In the subgroup also treated with streptokinase, aspirin was withheld. In-hospital mortality was 4.6% in the UFH group and 8.8% in the control group, and a reduction in stroke was observed. Therefore, UFH is recommended for these patients at high risk for systemic arterial emboli, regardless of the fibrinolytic agent given. A LMWH may be used in place of UFH. Initial anticoagulation with UFH or a LMWH should be followed by warfarin in patients at high risk for systemic emboli (see Section 7.12.11 for additional discussion).

The previous ACC/AHA guidelines on acute MI (744) and the American College of Chest Physicians' guidelines (746) recommended 7500 U of subcutaneous UFH twice per day. The empirical basis for this recommendation was the demonstration that DVT was reduced from 12% to 4% in an overview of 3 randomized controlled trials (747). Continued adherence to this practice may be useful, although routine earlier mobilization and use of aspirin may make this treatment unnecessary.

7.4.6. 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)***

The use of oxygen in patients presenting with STEMI is discussed in Section 6.3.1.1. In view of its expense (approximately $70 per day), there is little justification for continuing its routine use beyond 6 hours in uncomplicated cases.

Pulse oximetry is now routine for continuous monitoring of oxygen saturation and is helpful for providing early warning of hypoxemia. In patients with oxygen saturation less than 90%, supplemental oxygen by nasal prongs is usually administered, especially if the patient is experiencing ongoing or intermittent ischemia. This therapy is based on experimental data that suggest that normal levels of oxygen reduce infarct size. In patients with severe heart failure, pulmonary edema, or mechanical complications of STEMI, significant hypoxemia may require continuous positive pressure breathing or endotracheal intubation and mechanical ventilation.

7.5. Estimation of Infarct Size

Measurement of infarct size is an important element in the overall care of patients with STEMI. The extent of infarction bears a direct relationship to prognosis, assists in establishing the efficacy of reperfusion therapy, guides both short- and long-term therapeutic decision making, and provides a useful surrogate for the investigation of novel experimental therapies.

There are 5 major modalities that can be applied to sizing MI. A discussion of each follows.

7.5.1. ECG 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)***

The extent of ST-segment deviation on the baseline ECG provides a semiquantitative measure of the amount of jeopardized myocardium and an estimate of the subsequent infarct size likely to ensue in a nonreperfused population. With a QRS scoring system based on the duration and amplitude of individual waveforms within the QRS complex, the size of the infarction can be estimated from a point score derived and weighted from the 12-lead ECG (748). Each point so derived represents approximately 3% of the LV, and the utility of this approach has been validated in postmortem studies of patients with confirmed MI (749). This method, however, is time consuming and is limited in patients with concomitant LV hypertrophy or fascicular or bundle-branch block and when major ST-segment shift distorts the appearance of the QRS complex.

In the fibrinolytic era, simple characterization of the presence or absence of the Q wave has also been used. In the early convalescent period after fibrinolytic therapy, the 20% of patients in the GUSTO angiographic study who did not develop Q waves had better global and regional LV function and improved 2-year survival (6.3% versus 10.1% for patients with developed Q waves; p equals 0.02) (750).

7.5.2. Cardiac Biomarker Methods

The most widely accepted method for quantifying infarction has been the use of serial CK and the CK-MB isoenzyme. With a mathematical formulation based on rates of degradation in specific compartments, the rate of myocardial biomarker release, its volume of distribution, and its clearance rate, it is possible to estimate the quantity of myocardium infarcted (751). Reasonable correlations have been established with anatomic estimates derived from postmortem human studies (752). Whereas other biomarkers of myocar-

dial necrosis exist, such as myoglobin and lactate dehydrogenase, the highly sensitive cardiac troponins (I or T) have greater myocardial tissue specificity and higher sensitivity than conventional biomarkers. Measurement of cardiac troponin T at 72 hours provides an estimate of infarct size in patients with STEMI who do and do not receive reperfusion therapy (753,754). In a consensus document of the Joint European Society of Cardiology and the ACC, the use of cardiac troponins was supported for the assessment of MI. The Joint Committee has emphasized that high-sensitivity cardiac biomarkers, such as troponins, can identify patients with small areas of myocardial necrosis weighing less than 1.0 g (755).

7.5.3. Radionuclide Imaging

The most comprehensive assessment of STEMI with radionuclide imaging was developed with the Technetium sestamibi SPECT approach (756). This technique has been validated extensively and offers the opportunity for both early and late imaging to initially assess the area of ischemic risk as opposed to the ultimate infarct size. This approach is well delineated in the ACC/AHA/ASNC Guidelines on Cardiac Radionuclide Imaging (239). Radionuclide angiography with a variety of radiolabeled isotopes can also provide an estimate of regional and global LV function.

7.5.4. Echocardiography

Global and regional LV function provides an assessment of the functional consequences of STEMI and ischemia. Such measures may be enhanced by an assessment of the extent of regional systolic wall thickening. Readers are referred Section 7.11.1.2 and to the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography (226).

7.5.5. Magnetic Resonance Imaging

Measurement of infarct size with magnetic resonance imaging is a promising new technique that affords enhanced spatial resolution, thereby permitting more accurate assessment of both the transmural and circumferential extent of infarction (757). However, additional experience and comparison with other methods of assessing infarct size are required before any clinical recommendations can be provided.

7.6. Hemodynamic Disturbances

7.6.1. 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 mmHg).** ***(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)***

Measurements made via pulmonary artery catheter readings may be helpful in the management of STEMI and concomitant hemodynamic instability, including low cardiac output, hypotension, persistent tachycardia, pulmonary edema, and apparent cardiogenic shock. In the patient with hypotension and tachycardia, the pulmonary artery catheter can assist in the differentiation of 1) inadequate intravascular volume, with a resultant low left-sided filling pressure; 2) adequate intravascular volume and a high left-sided filling pressure due to extensive LV dysfunction; and 3) low left-sided filling pressure with elevated right atrial pressure consistent with RV infarction (758). Treatment of the former is prompt expansion of intravascular volume (with normal saline), whereas management of the latter often includes diuresis, inotropic support, afterload reduction, or other sup-

portive measures. In those with extensive LV dysfunction, a pulmonary artery catheter can be used to monitor therapeutic efforts to adjust the left-sided filling pressure so as to maximize cardiac output at the lowest possible filling pressure (758). In some patients, these sophisticated manipulations of intracardiac pressures and cardiac output are facilitated by information provided by a pulmonary artery catheter.

Although the pulmonary artery catheter is quite safe when used by experienced operators, its use has a recognized association with adverse events, including ventricular tachyarrhythmias (during its manipulation) and pulmonary hemorrhage or infarction. Transient right bundle-branch block may develop, which can lead to heart block in those with preexisting LBBB. In addition, it causes some patient discomfort and requires that the patient be relatively immobile. Because the pressure waveform recorded from the catheter tip may be distorted, the clinician should routinely examine the actual waveform rather than rely on the digital display of pressure. Because of the risk of infection, pulmonary artery catheters generally should not remain in the same site for more than 4 to 5 days. The catheter should not be inserted if the patient quickly responds to other interventions or if treatment is expected to be futile. The catheter should be removed expeditiously when it is no longer needed to monitor therapy.

The diagnosis of acute mechanical complications (MR, ventricular septal defect, myocardial rupture) usually can be diagnosed quickly and safely in the ED by transthoracic echocardiography. However, the ordering and performing of an echocardiogram should not delay transfer of a hemodynamically unstable patient to the interventional cardiology laboratory, where hemodynamic stabilization, diagnosis, and treatment can usually best be initiated. Similarly, insertion of a pulmonary artery catheter in the CCU should not delay transfer of the patient to the interventional cardiology laboratory if indicated.

Insertion of a pulmonary artery catheter to measure hemodynamics in patients developing progressive CHF or hypotension may permit the early diagnosis of a preshock state in which appropriate support can prevent the onset of cardiogenic shock (759). Before PCI is performed for cardiogenic shock, the interventional cardiologist should insert a pulmonary artery catheter to maximize the hemodynamic status of the patient and to diagnose unrecognized mechanical complications. After reperfusion therapy, if shock does not rapidly reverse, the pulmonary artery catheter may be used to guide diuretic, inotropic, and vasopressor agents in hemodynamically unstable patients while stunned myocardium is recovering. Unfortunately, there are no data from randomized controlled trials testing whether or not hemodynamic monitoring alters clinical outcome in STEMI.

It is possible that therapeutic interventions in response to erroneous data or inappropriate maneuvers in response to accurate data contribute to the excess mortality rates previously associated with pulmonary artery catheter use (760-762). Clinicians should understand the multiple determinants of pulmonary capillary wedge pressure (PCWP) to avoid equating filling pressure with intravascular volume (compliance, veno-vasodilation, intrathoracic pressure, position, volume). Dynamic changes in ventricular compliance and the use of vasodilating medications result in rapid changes in PCWP that do not reflect intravascular volume. For example, pulmonary artery catheter placement after intravenous nitroglycerin administration for pulmonary edema may reflect PCWP less than 15 mm Hg despite marked elevation 1 hour earlier. An acute ischemic episode may raise PCWP substantially without a concomitant change in volume.

All CCUs should have sufficient equipment and skilled personnel to monitor intra-arterial pressure. Such monitoring is useful in all hypotensive patients, particularly those with cardiogenic shock. Long-term monitoring is best accomplished through the radial artery, although the brachial or femoral arteries may be used as alternatives. Perfusion of the limb or hand distal to the catheter site must be examined carefully and periodically for evidence of ischemia. Intra-arterial and central catheters can be left in place with a sterile occlusive dressing. Before insertion, the site should be adequately prepared under sterile conditions. Antibacterial ointments are no longer recommended. Because of the risk of arterial thrombosis and infection, intra-arterial catheters generally should not remain in the same arterial site for longer than 4 to 5 days (763).

7.6.2. Hypotension

Class I

1. **Rapid volume loading with an intravenous 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 administered 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)***

Hypotension (systolic pressure less than 90 mm Hg or 30 points below previous systolic arterial pressure) can result from hypovolemia, arrhythmias, RV or LV failure, mechanical complications of MI, or superimposed complications, such as sepsis or pulmonary embolism. Hypovolemia is a common occurrence and may be due to inadequate intake, diaphoresis and vomiting, overdiuresis, excessive use of vasodilators, or inappropriate reflex peripheral vasodilation. Hemorrhage is an increasingly common problem associated with the use of invasive procedures, fibrinolytics, antiplatelet agents, and anticoagulant agents. Therefore, rapid volume

loading is recommended as an initial therapeutic strategy in all patients without clinical evidence for volume overload. Persistent hypotension should be evaluated with an echocardiogram to define the cardiac anatomy and with a hemoglobin measurement. Correction or control of rhythm disturbances or conduction abnormalities often reverses hypotension. In patients with inotropic failure, vasopressors and inotropic agents are required. Vasopressor agents, including high-dose dopamine and norepinephrine, have alpha-vasoconstricting properties, whereas inotropic agents such as dobutamine have beta-receptor–stimulating properties. Norepinephrine and dopamine have both vasopressor and inotropic properties. When blood pressure is low, dopamine is the agent of first choice. If the patient is markedly hypotensive, intravenous norepinephrine, which is a more potent vasoconstrictor with less potential for tachycardia, should be administered until systolic arterial pressure rises to at least 80 mm Hg, at which time a change to dopamine may be attempted, initiated at 2.5 to 5 mcg/kg/min and titrated as needed to 5 to 15 mcg/kg/min. Once arterial pressure is brought to at least 90 mm Hg, intravenous dobutamine may be given simultaneously in an attempt to reduce the rate of the dopamine infusion. In addition, consideration should be given to initiating intra-aortic balloon counterpulsation. (See Section 7.6.1.)

7.6.3. Low-Output State

Class I

1. **Left ventricular 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)***

A preshock state of hypoperfusion with normal blood pressure may develop before circulatory collapse and is manifested by cold extremities, cyanosis, oliguria, or decreased mentation (759). Hospital mortality is high, so these patients should be aggressively diagnosed and treated as though they had cardiogenic shock. The initial pharmacological intervention for low cardiac output is often a dobutamine infusion. Intra-aortic counterpulsation therapy may be required to improve coronary artery perfusion pressure if hypotension is present. If the blood pressure permits, afterload-reducing agents should be added to decrease cardiac work and pulmonary congestion. Coronary artery revascularization of ischemic myocardium with either PCI or CABG has been shown to decrease mortality in patients with cardiogenic shock and is strongly recommended in suitable candidates (184,301). Likewise, patients with VSR, papillary muscle rupture, or free wall rupture with pericardial tamponade may benefit from emergency surgical repair.

7.6.4. 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 for 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 of 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 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)***

Left ventricular filling pressures, and hence PCWP, may rise rapidly after acute coronary occlusion. This rise is due to acute systolic or diastolic dysfunction that may be associated with superimposed MR. The rise in PCWP leads to rapid redistribution of fluid from the intravascular space into the extravascular space (lung interstitium and alveoli). The presence of any pulmonary congestion on examination or X-ray increases the risk of dying, and pulmonary edema is associated with a 20% to 40% 30-day mortality rate even in the fibrinolytic era (28,240,242,764).

Immediate management goals include adequate oxygenation and preload reduction to relieve pulmonary congestion. Because of sympathetic stimulation, the blood pressure should be elevated in the presence of pulmonary edema. Patients with this appropriate response can typically tolerate the required medications, all of which lower blood pressure. However, iatrogenic cardiogenic shock may result from aggressive simultaneous use of agents that cause hypotension, initiating a cycle of hypoperfusion-ischemia. If acute pulmonary edema is not associated with elevation of the systemic blood pressure, impending cardiogenic shock must be suspected. If pulmonary edema is associated with hypotension, cardiogenic shock is diagnosed. Those patients often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion (see Section 7.6.5 and Figure 26).

Pulmonary edema may occur as an acute event with the onset of STEMI or reinfarction or as the culmination of slowly progressive CHF over the first several days after infarction. Acute pulmonary edema on presentation with STEMI may occur in a patient with prior myocardial damage and systolic dysfunction, with or without a prior diagnosis of CHF. Alternatively, it may develop in patients with a first STEMI, especially those with preceding diastolic dysfunction due to hypertension or diabetes. Pulmonary edema days after STEMI or on presentation in patients who have prior CHF or LV dysfunction is often associated with hypervolemia. In contrast, patients who present with pulmonary edema without prior LV dysfunction (and who have not received fluid administration) usually have a normal total body sodium and fluid status. The acute redistribution of fluid into the lungs results in relative intravascular volume depletion in the early phase. Acute diuresis and agents that induce hypotension can precipitate cardiogenic shock.

The cause of pulmonary edema (i.e., systolic, diastolic, or a mechanical complication [MR or VSR]) should be assessed rapidly with a 2-dimensional echocardiograph with color flow Doppler. Indications for right heart catheterization are reviewed in Section 7.6.1. On the basis of data that high-risk patients derive greater benefit from PCI than from fibrinolytic therapy, primary PCI is preferred when available for those who present with pulmonary edema complicating STEMI. There are no randomized trials that assess this comparison. However, analysis of the GUSTO-IIB trial shows similar relative and greater absolute benefit from PCI for Killip class 2 to 3 patients (765). The NRMI registry showed a marked benefit of PCI compared with fibrinolysis for patients with CHF (447). Coronary angiography and revascularization, based on the anatomy, should be performed when late CHF complicates the hospital course. Mechanical ventilation may be required during angiography and PCI, especially for primary PCI during STEMI.

Management includes the use of agents that acutely reduce preload (i.e., nitrates, morphine sulfate, and diuretics) (Figure 28) (766), and avoidance of acute administration of negative inotropic agents (i.e., beta-blockers and calcium channel antagonists). Nitrates are initially administered by sublingual tablets or spray nitroglycerin followed by intravenous nitroglycerin. Intravenous nitroglycerin is a venodilator that acutely reduces ventricular filling pressures. At high doses, it dilates arterioles. It is effective at relieving pulmonary congestion and ischemia and may be used in patients who have normal or elevated systemic arterial pressure. A 10- to 20-mcg bolus should be administered, followed by 10 mcg per minute, increased by 5 to 10 mcg per minute every 5 to 10 minutes until dyspnea is relieved, the mean arterial pressure is lowered by 10% in normotensive patients or 30% in hypertensive patients, or until the heart rate increases by more than 10 bpm. Loop diuretics (furosemide, torsemide, or bumetanide) should be initiated in low to intermediate doses only in patients with associated hypervolemia (see above). Low doses should be used unless there is renal insufficiency, chronic diuretic use, or the presence of chronic CHF and hypervolemia as described above. Typical furosemide doses range from 20 to 80 mg IV (0.5 to 1.0 mg/kg).

Angiotensin converting enzyme inhibitors are indicated for patients with pulmonary congestion. Oral ACE inhibitors, preferably a short-acting agent such as captopril, beginning with 1 to 6.25 mg, should be instituted early in normotensive or hypertensive patients. The dosage may be doubled with each subsequent dose as tolerated up to 25 to 50 mg every 8 hours, then changed to a long-acting agent. Although the risk of hypotension and shock after vasodilator or diuretic administration during the acute phase of MI is substantial for those without a hypertensive response to pulmonary edema, the risk is lower in the late phase after MI. Hence, most patients can tolerate ACE inhibitors before discharge. For patients who presented with CHF complicating MI, ramipril administration between days 3 and 10 significantly reduced 30-day

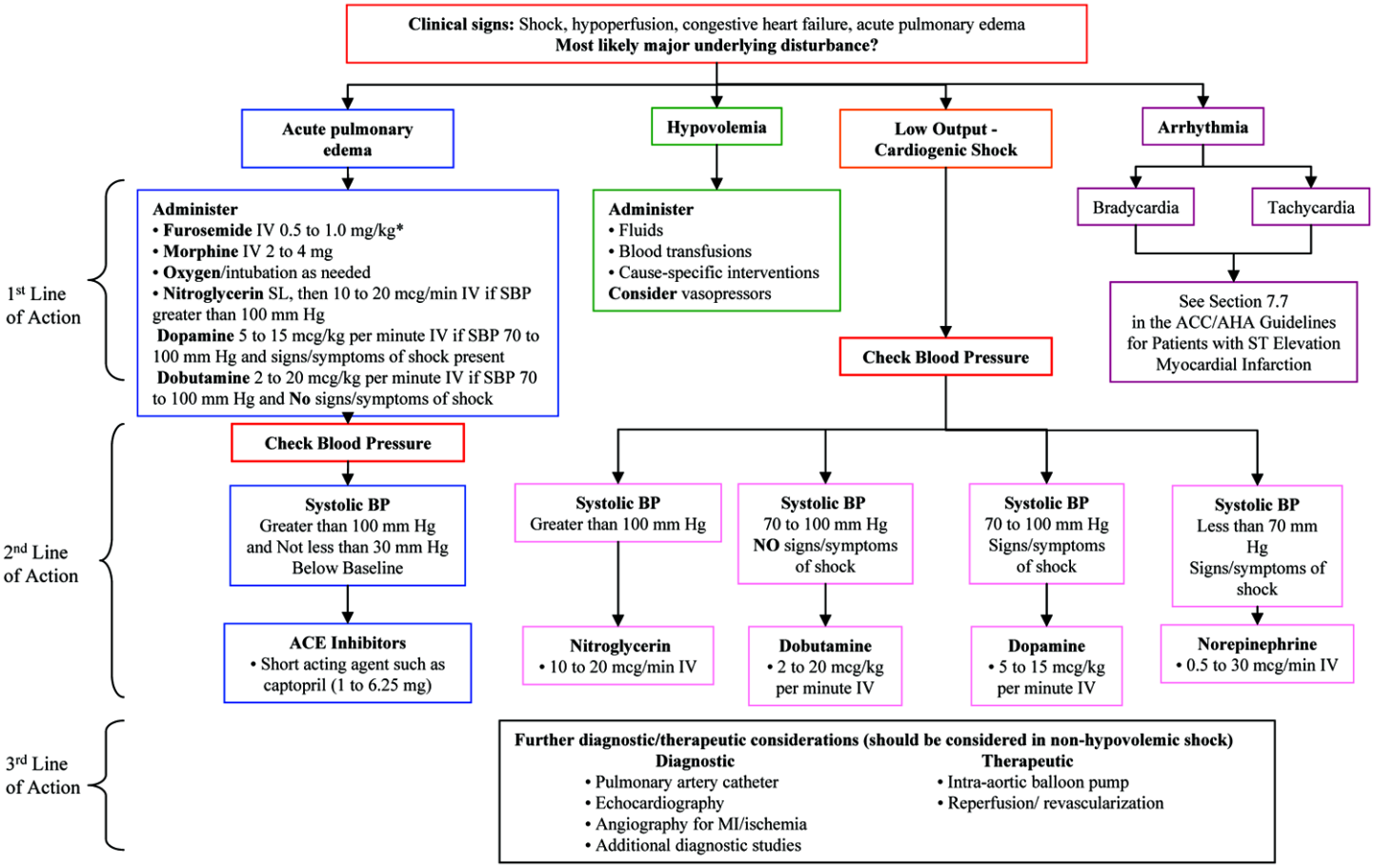


Figure 28. Emergency management of complicated ST-elevation myocardial infarction (STEMI). The emergency management of patients with cardiogenic shock, acute pulmonary edema or both is outlined. IV = intravenous; SL - sublingual; SBP = systolic BP; BP = blood pressure; ACE = angiotensin converting enzyme; MI = myocardial infarction. *Furosemide less than 0.5 mg/kg for new onset acute pulmonary edema without hypovolemia. 1 mg/kg for acute or chronic volume overload, renal insufficiency. Nesiritide has not been studied adequately in patients with STEMI. Combinations of medications (e.g., dobutamine and dopamine) may be used. Modified with permission from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Part 7: The Era of Reperfusion. Section 1: Acute Coronary Syndromes (Acute Myocardial Infarction). Circulation 2000;102: I-172 - I-216 (766).

mortality (relative hazard 0.73; 95% CI 0.602 to 0.89; p greater than 0.002) in 2006 patients in the Acute Infarction Ramipril Efficacy Study (767). Given the good tolerability of ACE inhibition within 24 hours of MI in the ISIS-4 and GISSI-3 (lisinopril) studies and the beneficial effects on early infarct expansion, it is recommended that ACE inhibitors be initiated early for those who have pulmonary congestion. However, hypotension should be avoided, particularly during and immediately after reperfusion therapy (767,768). Routine intravenous enalapril is not recommended (769) unless severe hypertension is present. ACE inhibitors are the only adjunctive medication (beyond aspirin and reperfusion therapy) demonstrated to reduce 30-day mortality when CHF complicates STEMI. Therefore, if blood pressure limits use of vasodilators, ACE inhibitors are preferred. Intravenous sodium nitroprusside substantially reduces afterload and preload; however, its use has been associated with coronary steal. Digitalis has no role in the management of pulmonary edema complicating STEMI unless rapid AF is present. Nesiritide (synthetic natriuretic brain peptide) is a new vasodilator agent that promotes diuresis in patients with volume overload and decompensated chronic CHF (class 3 to 4) (770). It has not been investigated in STEMI and is not indicated for treatment of pulmonary edema in these patients. Nesiritide is a potent vasodilator and may result in hypotension, particularly in patients with STEMI, in whom CHF usually is not due to volume overload.

An aldosterone antagonist, eplerenone, was found to be effective for secondary prevention of death and recurrent hospitalization in patients 3 to 14 days after MI with CHF and LVEF less than 0.40. Spironolactone has been demonstrated to improve survival in a population of patients with chronic CHF, which includes those with remote MI (722) (see Section 7.12.6). In contrast to the recommendation to avoid initiation of beta-blockade during pulmonary edema, beta-blockers are strongly recommended before hospital discharge for secondary prevention of cardiac events (273). The initial dose and titration should be based on clinical heart failure status and LVEF. For patients who remain in heart failure during the hospitalization, a low dose should be initiated and gradually titrated as an outpatient, per CHF guide-

lines (771). This is supported by the beneficial effects of beta-blockade in patients with LV dysfunction after STEMI (771).

See also Sections 7.4.3 (hospital phase) and 7.12.6 (secondary prevention) for recommendations on ARBs.

7.6.5. 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 who 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 who 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)***

Cardiogenic shock in patients with STEMI is most commonly (75% of cases) caused by extensive LV dysfunction, but important other causes include mechanical complications (acute severe MR, VSR, and subacute free-wall rupture with tamponade). Important conditions that may mimic cardiogenic shock include aortic dissection and hemorrhagic shock. Echocardiography with color flow Doppler is extremely useful to assess the cause of shock. (See Section 7.6.1 for discussion on hemodynamic assessment.)

Nonrandomized studies have suggested that mechanical reperfusion of occluded coronary arteries by PCI or CABG may improve survival in patients with MI and cardiogenic shock. In large clinical trials, such patients have an in-hospital survival rate that ranges from 20% to 50% when treated with intravenous fibrinolytic therapy (482,483,772,773). In other case series, mechanical reperfusion with PCI has been reported to result in hospital survival rates as high as 70%, but selection bias influenced these findings. However, a multicenter, prospective, randomized study confirmed this general approach (184). The SHOCK trial tested the hypothesis that emergency revascularization for cardiogenic shock due to an ST-elevation/Q-wave or new LBBB MI would result in reduction in all-cause 30-day mortality compared with initial medical stabilization and delayed revascularization as clinically determined. In the SHOCK trial, cardiogenic shock was defined as clinical evidence of systemic hypoperfusion with systolic blood pressure less than 90 mm Hg for at least 30 minutes (or the need for supportive measures to maintain systolic blood pressure greater than 90 mm Hg), cardiac index of no more than 2.2 L/min/m^2 and PCWP of at least 15 mm Hg.

In the SHOCK trial, 152 patients were randomly assigned to the emergency revascularization strategy, and 150 patients were assigned to a strategy of initial medical stabilization. The 30-day mortality rate for emergency revascularization patients was 46.7% versus 56.0% for initial medical stabilization patients (95% CI minus 20.5 to plus 1.9%, p equals 0.11). However, the mortality rate at 6 and 12 months (secondary end points) was significantly lower in the emergency revascularization group (53.3% versus 66.4%, p less than 0.03, 12 months) (184,494). The prespecified subgroup analysis of patients less than 75 years old showed a 15.4% absolute reduction in the primary end point at 30 days (initial medical stabilization group 56.8% versus emergency revascularization group 41.4%, p less than 0.01), whereas no treatment benefit was apparent for the 56 patients greater than 75 years old. Intra-aortic balloon pump support was used in 86% of both groups; 63% of the initial medical stabilization group received thrombolytic agents, and 25% underwent delayed revascularization (Figure 29) (184). The (S)MASH study [(Swiss) Multicenter Trial of Angioplasty for Shock] randomly assigned 55 refractory shock patients to either PCI or conventional care. The mortality rate in the PCI group was 9 absolute percentage points lower at 30 days (69% versus 78%) than in the conventional therapy group but did not reach statistical significance (495). The group difference was similar to that observed at 30 days in the SHOCK trial (494).

Given the large overall treatment benefit of 13 lives saved per 100 patients treated, emergency revascularization is recommended for those less than 75 years who are suitable for revascularization. Patients with life-shortening illnesses, no vascular access, previously defined coronary anatomy that was unsuitable for revascularization, anoxic brain damage, and prior cardiomyopathy were excluded from the trial. For those enrolled, the treatment benefit was similar for all other subgroups examined: diabetics, women, prior MI or hypertension, and early or late developing shock. The elderly pose a special problem. There were only 56 patients 75 years of age or older in the SHOCK trial, and firm conclusions can-

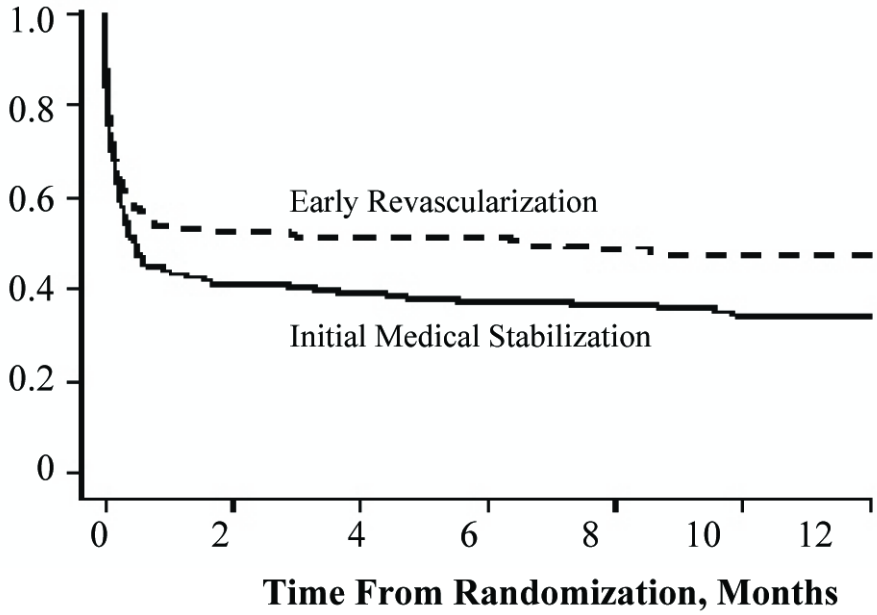


Figure 29. Kaplan-Meier survival of cardiogenic shock after early revascularization curve 1-year postrandomization. Survival estimates for early revascularization (n=152) and initial medical stabilization (n=149) groups. Log-rank test P = 0.04. Reprinted with permission from Hochman et al. JAMA 2001;285:190-2. Copyrighted © 2001, American Medical Association. All rights reserved (184).

not be drawn. The mortality rate for the elderly patients assigned to initial medical stabilization was similar to younger patients assigned to initial medical stabilization and was therefore unexpectedly low (53.1%). Imbalances in baseline characteristics of the 56 elderly patients assigned to the emergency revascularization versus initial medical stabilization groups may also have played a role in the apparent lack of treatment effect (301). Those elderly patients (n equals 277) who were clinically selected for early revascularization (17% of the cohort) in the larger, nonrandomized SHOCK registry had a marked survival benefit compared with those with late or no revascularization, even after covariate adjustment and exclusion of early deaths (496). Two other large registries reported a substantial survival benefit for the elderly who were clinically selected on the basis of physician judgment. In these 2 registries, 16% to 33% of the elderly were selected for an invasive strategy (497,498). Although not reported, selection is typically based on prior functional status, comorbidity, suitability for revascularization, and patient and family preferences. An analysis of Medicare patients admitted to hospitals with or without revascularization capability reported no significant reduction in mortality by institution type for patients who presented in shock (0.6%) (774). They did not examine the much larger cohort (approximately 7%) who develop shock. The elderly require individualized judgments, and it is reasonable to consider those with a good functional status and who agree to an aggressive strategy for early revascularization.

Interventions should be performed as soon as possible. However, the time window for early revascularization, as defined in the SHOCK trial, extends to shock that develops up to 36 hours after MI and revascularization within 18 hours of shock. Triple-vessel disease (60%) and left main disease (20%) are often present when shock complicates STEMI. Coronary artery bypass graft surgery is the preferred mode of revascularization for many of these patients on the basis of unsuitability for PCI and to achieve complete revascularization, unload the heart, and administer cardioprotective agents (775,776). The SHOCK trial recommended emergency CABG within 6 hours of randomization for those with severe 3-vessel or left main coronary artery disease. Among the group of patients who underwent emergency early revascularization, 60% received PCI, and 40% had CABG; the 30-day mortality rate was 45% and 42%, respectively. Thirty-day outcome was similar despite more severe coronary artery disease and twice the frequency of diabetes in those who underwent CABG. This is in contrast to the 69% in-hospital mortality rate reported for those with 3-vessel disease who underwent PCI for shock (777). Perhaps distal embolization in the non–infarct-related artery is not tolerated by patients in shock. For moderate 3-vessel disease, the SHOCK trial recommended proceeding with PCI of the infarct-related artery, followed by delayed CABG for those who stabilized (Figure 26) (494,502).

It is recommended that patients who arrive at the hospital in cardiogenic shock (15% of cases) or who develop cardiogenic shock after arrival at the hospital (85%) be transferred to a regional tertiary care center with revascularization facilities and experience with these patients. (The SHOCK trial included both transferred [55%] and directly admitted patients and demonstrated the same relative treatment benefit). If skilled personnel are available, IABP placement before transport will help stabilize the patient. If the patient presents in shock within 3 to 6 hours of MI onset and delays in transport and intervention are anticipated, fibrinolytic therapy and IABP may be initiated. Nonrandomized studies suggest that this combination is beneficial (778), and a small randomized trial observed a trend toward benefit for those in

classic shock, with acceptable complication rates. Fibrinolytic therapy should be administered to those patients who are not candidates for early revascularization and who do not have a contraindication to fibrinolysis.

When shock has resolved, ACE inhibitors and beta-blockers, initiated in low doses with progressive increases as recommended in the ACC/AHA Guidelines for the Evaluation and Management of Heart Failure, should be administered before discharge (771). (See Section 7.6.7.6 for discussion of mechanical support for the failing heart.)

7.6.6. Right Ventricular Infarction

Class I

1. **Patients with inferior STEMI and hemodynamic compromise should be assessed with a right precordial V_4R 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 (226)). *(Level of Evidence: B)***
2. **The following principles apply to therapy for patients with STEMI and RV infarction and ischemic dysfunction:**
   a. **Early reperfusion should be achieved if possible. *(Level of Evidence: C)***
   b. **Atrioventricular synchrony should be achieved, and bradycardia should be corrected. *(Level of Evidence: C)***
   c. **Right ventricular 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. **Right ventricular 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)*

Right Ventricular Infarction and Dysfunction. Right ventricular infarction encompasses a spectrum of disease states ranging from asymptomatic mild RV dysfunction through cardiogenic shock. Most patients demonstrate a return of normal RV function over a period of weeks to months, which suggests that RV stunning, rather than irreversible necrosis, has occurred. In this sense, RV ischemia can be demonstrated in up to half of all inferior STEMIs, although only 10% to 15% of patients show classic hemodynamic abnormalities of clinically significant RV infarction (780,781).

Right ventricular infarction with hemodynamic abnormalities accompanying inferior STEMI is associated with a significantly higher mortality (25% to 30%) and thus identifies a high-risk subgroup of patients with inferior STEMIs (6%) who should be considered high-priority candidates for reperfusion (780). One group of investigators reported a 31% in-hospital mortality rate in patients with inferior STEMIs complicated by RV infarction compared with 6% in patients who had an inferior STEMI without RV involvement (780). An analysis of patients with predominant RV infarction and cardiogenic shock from the SHOCK trial registry demonstrated an unexpectedly high mortality rate similar to that for patients with LV shock (53.1% versus 60.8%) (782). The treatment of patients with RV ischemic dysfunction is different and, in several ways, diametrically opposed to management of LV dysfunction.

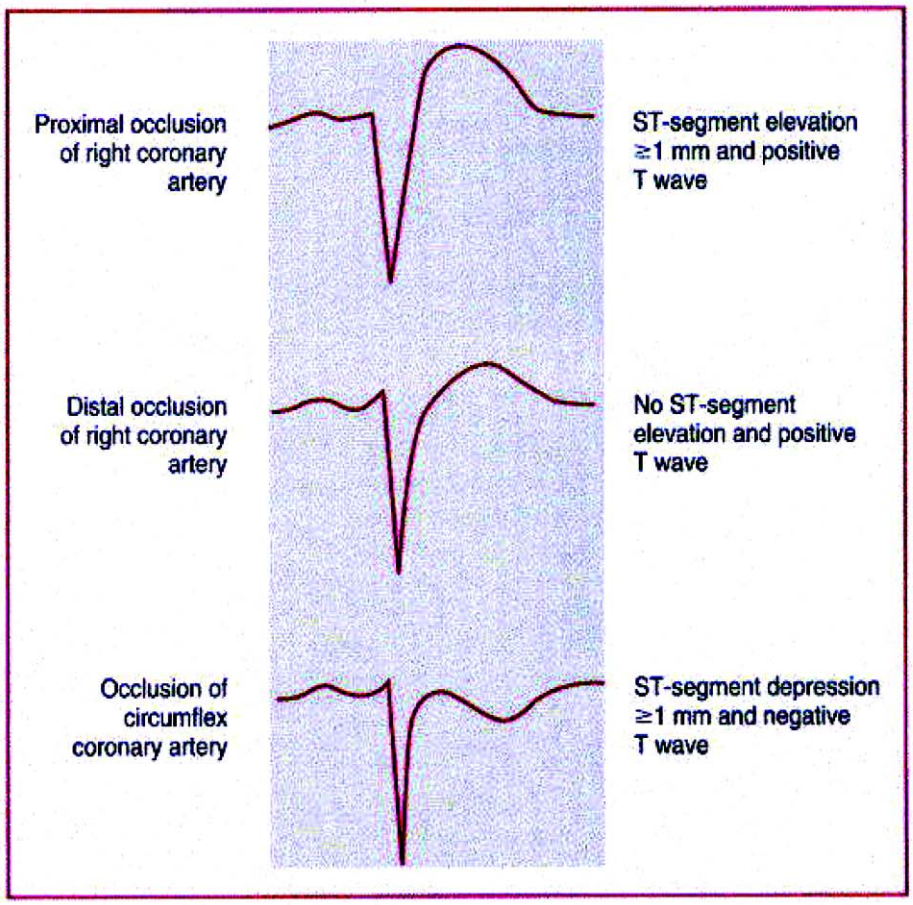
Anatomic and Pathophysiological Considerations. The right coronary artery usually supplies most of the RV myocardium; thus, occlusion of this artery proximal to the RV branches will lead to RV ischemia (783). Hemodynamically significant RV infarctions occur almost exclusively in the setting of inferior STEMIs (784). Because the RV has a much smaller muscle mass than the LV, owing to the lower vascular resistance of the pulmonary circuit, myocardial oxygen demand is significantly less than that of the LV (785). Coronary perfusion of the RV occurs in both systole and diastole (785). The RV also has a more favorable oxygen supply-demand ratio than the LV because of the more extensive collateral flow from left to right (786,787). These factors likely explain the absence of hemodynamically significant RV ischemia in most patients with proximal right coronary artery occlusions, as well as improvement in RV function observed in the majority of patients after RV ischemia (788).

The severity of the hemodynamic derangements associated with RV ischemia is related to 1) the extent of ischemia and subsequent RV dysfunction, 2) the restraining effect of the surrounding pericardium, and 3) interventricular dependence related to the shared interventricular septum. When the RV becomes ischemic, it dilates acutely, which results in increased intrapericardial pressure caused by the restraining forces of the pericardium. As a consequence, there is a reduction in RV systolic pressure and output, decreased LV preload, a reduction in LV end-diastolic dimension and stroke volume, and a shifting of the interventricular septum toward the LV (789). Because of this RV systolic and diastolic dysfunction, the pressure gradient between the right and left atria becomes an important driving force for pulmonary perfusion. Factors that reduce preload (volume depletion, diuretics, nitrates) or diminish augmented right atrial contraction (concomitant atrial infarction, loss of AV synchrony) and factors that increase RV afterload (concomitant LV dysfunction) are likely to have profoundly adverse hemodynamic effects (790-794). Goldstein and coworkers (791,794) demonstrated the importance of a paradoxical interventricular septal motion that bulges in piston-like fashion into the RV, generating systolic force, which allows pulmonary perfusion. The loss of this compensatory mechanism, with concomitant septal infarction, may result in further deterioration in patients with RV ischemia.

Clinical Diagnosis. Evidence of RV ischemia/infarction should be sought in all patients with inferior STEMI. The clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure in the setting of a STEMI is characteristic of RV ischemia/infarction. Although specific, this triad has a sensitivity of less than 25% (795). Distended neck veins alone or the presence of Kussmaul's sign (distention of the jugular vein on inspiration) are both sensitive and specific for RV ischemia/infarction in patients with a STEMI (796). These findings may be masked in the setting of volume depletion and may only become evident after adequate volume loading. Right heart catheterization may be helpful in diagnosing RV ischemia/infarction. A right atrial pressure of 10 mm Hg or greater and greater than 80% of pulmonary wedge pressure is a relatively sensitive and specific finding in patients with RV ischemia/infarction (797).

Patients with RV hypertrophy, commonly due to the pulmonary hypertension associated with chronic obstructive pulmonary disease, have increased myocardial demand and may be more likely to suffer RV MI. Demonstration of 1-mm ST-segment elevation in lead V_1 and in the right precordial lead V_4R is the single most predictive ECG finding in patients with RV ischemia (798). The finding may be transient; half of patients show resolution of ST elevation within 10 hours of onset of symptoms (799). It is important for physicians to ensure that hospital personnel (house officer, nurse, technician) recording the ECG in this setting know how to properly record lead V_4R, especially in view of the variety of multilead recording systems available. All patients with inferior STEMI should be screened initially for this finding at the time of admission. Echocardiography can be helpful in patients with suspicious but nondiagnostic findings (226). It can show RV dilation and asynergy, abnormal interventricular and interatrial septal motion, and even right to left shunting through a patent foramen ovale (800-802). Right to left shunting should be suspected when persistent hypoxia is not responsive to supplemental oxygen (802).

Management of RV Ischemia/Infarction. Treatment of RV ischemia/infarction includes early maintenance of RV preload, reduction of RV afterload, inotropic support of the dysfunctional RV, and early reperfusion (Figure 30) (257,803). Because of their influence on preload, drugs routinely used in management of LV infarctions, such as nitrates and diuretics, may reduce cardiac output and produce severe hypotension when the RV is ischemic. Indeed, a common clinical presentation is profound hypotension after administration of sublingual nitroglycerin, with the degree of hypotension often out of proportion to the ECG severity of the infarct. Volume loading with normal saline alone often resolves



Clinical findings:
- **Shock with clear lungs, elevated JVP**
- **Kussmaul sign**

Hemodynamics:
- **Increased RA pressure (y descent)**
- **Square root sign in RV tracing**

ECG:
- **ST elevation in R sided leads**

Echo:
- **Depressed RV function**

Management:
- **Maintain RV preload**
- **Lower RV afterload (PA---PCW)**
- **Restore AV Synchrony**
- **Inotropic support**
- **Reperfusion**

Figure 30. Right ventricular infarction. JVP = jugular venous pressure; RA = right atrial; RV = right ventricular; PA = pulmonary artery; PCW = pulmonary capillary wedge. AV = atrioventricular. Modified with permission from Wellens. N Engl J Med 1999;340:381. Copyright © 1999 Massachusetts Medical Society. All rights reserved (803).

accompanying hypotension and improves cardiac output (804). The Trendelenburg position may effectively raise preload in patients who develop hypotension after vasodilator administration. Although volume loading is a critical first step in the management of hypotension associated with RV ischemia/infarction, inotropic support (in particular, dobutamine hydrochloride) should be initiated promptly if cardiac output fails to improve after 0.5 to 1 L of fluid have been given. Excessive volume loading may further alleviate the right-sided filling pressure and RV dilatation, resulting in decreased LV output (805-807) through shift of the interventricular septum for RV toward the LV.

Another important factor for sustaining adequate RV preload is maintenance of AV synchrony. High-degree heart block is common, occurring in as many as half of these patients (808). Atrioventricular sequential pacing leads to a significant increase in cardiac output and reversal of shock, even when ventricular pacing alone has not been of benefit (806). Atrial fibrillation may occur in up to one third of patients with RV ischemia/infarction (807) and has profound hemodynamic effects. Prompt cardioversion from AF should be considered at the earliest sign of hemodynamic compromise. When LV dysfunction accompanies RV ischemia/infarction, the RV is further compromised because of increased RV afterload and reduction in stroke volume (809). In such circumstances, the use of afterload-reducing agents or an intra-aortic counterpulsation device is often necessary to unload the LV and subsequently the RV. Fibrinolytic therapy and primary PCI with subsequent reperfusion have been shown to improve RV ejection fraction (793,810) and reduce the incidence of complete heart block (810-812).

Right ventricular failure secondary to an ischemic RV (either infarction or stunning) presents a particularly hazardous situation (813). The prototypical patient has an occluded right coronary artery proximal to the major RV branches and presents with an inferior MI with or without recognized RV failure (784,795,814-821). Angiography may demonstrate that the coronary anatomy is best treated surgically, but the opportunity for maximal benefit of an emergency operation (initial 4 to 6 hours) has often passed. There is substantial risk in operating after this small window of opportunity but before the recovery of RV function, which usually occurs at 4 weeks after injury (793). During this postinfarct month, the RV is at great risk for severe postoperative dysfunction, which often requires extraordinary levels of perioperative pharmacological and mechanical support and is associated with a very high mortality rate. The nonsurgical postinfarction patient can most often be supported with pacing, volume loading, and judicious inotropic administration (792). In the surgical setting, the RV takes on different characteristics. There is loss of the pericardial constraint immediately on exposing the heart, which results in acute dilation of the dysfunctional RV. The RV often fails to recover in this setting, even when state-of-the-art myocardial protection schemes and revascularization are used (822). The parallel effects of RV dilatation and dysfunction on LV diastolic and systolic function are magnified and may be associated with the need for high levels of support, inability to close the chest owing to cardiac dilation, need for ventricular assist devices, prolonged convalescence, transplantation, or death (792).

The best defense is an index of suspicion and recognition of the RV dysfunction by physical examination (795,810) ECG (right precordial leads), echocardiography, or radionuclide-gated blood pool study (793,810,823,824). If early PCI of the right coronary artery is indicated on the basis of angiography, this should be performed promptly. It is reasonable to delay coronary bypass surgery for 4 weeks to allow recovery of RV function.

Prognosis. The mere presence of RV ischemia/infarction that is evident by noninvasive criteria is associated with significantly increased short-term morbidity and mortality and may also influence long-term outcome (780,812,825). However, clinical and hemodynamic recovery often occur even in patients with RV dysfunction that persists for weeks or months (796,826-828). This return to normal may be due to improvement of concomitant LV dysfunction, which results in a reduction in RV afterload, or to a gradual stretching of the pericardium with amelioration of its restraining effect (826).

7.6.7. Mechanical Causes of Heart Failure/ Low-Output Syndrome

7.6.7.1. 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. Detailed characteristics of these mechanical defects are listed in Table 25 (829) (Figure 31). A precise diagnosis can usually be established with transthoracic or transesophageal echocardiography. A pulmonary artery monitoring catheter may also be useful in establishing the diagnosis of a mechanical defect and in its subsequent management. In VSR, oxygen saturation will be higher ("step-up") in the pulmonary artery than in the right atrium. With acute MR, a large C-V wave may be evident on the pulmonary artery wedge pressure tracing. However, a prominent V wave does not necessarily indicate the presence of MR and may also be present in patients with severe LV dysfunction associated with decreased left atrial compliance (830). A V wave may also be seen with VSR. In patients with free-wall ventricular rupture and subsequent pericardial tamponade, equalization of diastolic pressures may be seen.

Surgical consultation should be obtained when a mechanical defect is suspected so that an early decision regarding surgical management can be made. In general, prompt surgical repair is indicated in most cases, because medical treatment alone is associated with an extremely high mortality. Insertion of an IABP, particularly in patients with papillary muscle rupture or VSR, can help stabilize the patient. Although there is a need to minimize invasive procedures before early surgical correction of mechanical complications,

Table 25. Characteristics of Ventricular Septal Rupture (VSR), Rupture of the Ventricular Free Wall, and Papillary Muscle Rupture

Characteristic	VSR	Rupture of Ventricular Free Wall	Papillary Muscle Rupture
Incidence	1-3% without reperfusion therapy, 0.2-0.34% with fibrinolytic therapy, 3.9% among patients with cardiogenic shock	0.8-6.2%, Fibrinolytic therapy does not reduce risk; primary PTCA seems to reduce risk	About 1% (posteromedial more frequent than anterolateral papillary muscle)
Time course	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain, syncope, hypotension, arrhythmia, nausea, restlessness, hypotension, sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill (+), S_3, accentuated 2nd heart sound, pulmonary edema, RV and LV failure, cardiogenic shock	Jugulovenous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	VSR, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	Greater than 5 mm pericardial effusion not visualized in all cases, layered, high-acoustic echoes within the pericardium (blood clot), direct visualization of tear, signs of tamponade	Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe MR on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large V waves	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures among the cardiac chambers	No increase in oxygen saturation from the RA to RV, large V waves,* very high pulmonary-capillary wedge pressures

PTCA = percutaneous transluminal coronary angioplasty; RV = right ventricle/ventricular; LV = left ventricle/ventricular; RA = right atrium..
*Large V waves are from the pulmonary capillary wedge pressure.
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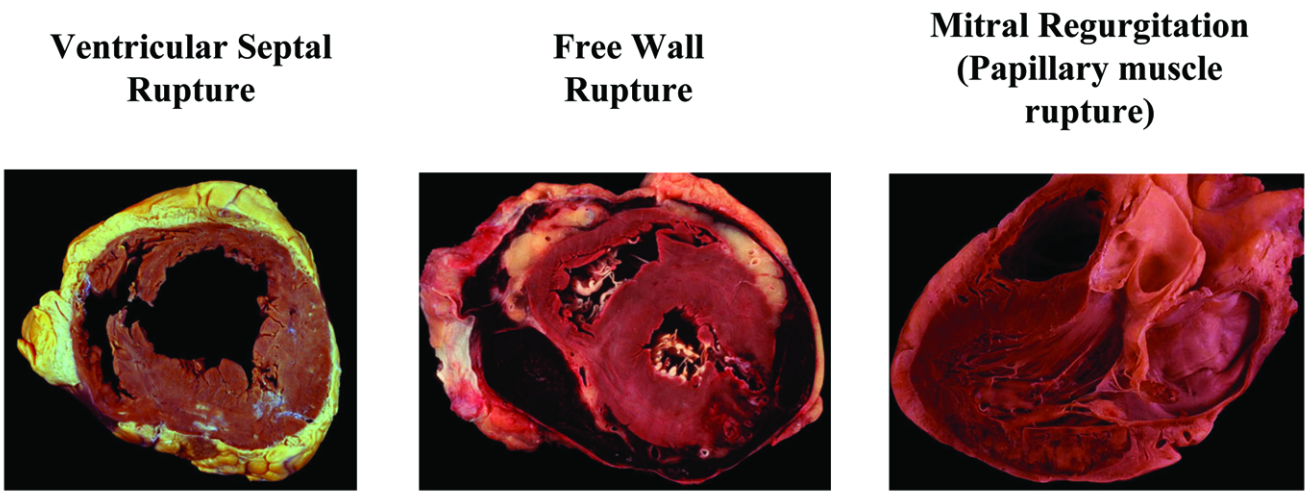

Figure 31. Mechanical complications of ST-elevation myocardial infarction (STEMI). See Table 25 for additional information. Images courtesy of William D. Edwards, M.D. (Mayo Clinic).

initial coronary angiography to assess coronary anatomy appears warranted in most cases of VSR and papillary muscle rupture. However, the evidence for the benefit of concomitant CABG associated with surgical repair of acute VSR is inconclusive (831). In the majority of patients, right and left heart catheterization are unnecessary unless other studies (e.g., echocardiography) are not clear in demonstrating a mechanical defect.

7.6.7.2. 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. **Coronary artery bypass graft surgery should be undertaken at the same time as mitral valve surgery. *(Level of Evidence: B)***

Severe MR after STEMI, accompanied by cardiogenic shock, has a poor prognosis. In the SHOCK trial registry, approximately 10% of patients with shock presented with severe MR and had an overall hospital mortality of 55% (832). Mortality with medical treatment only was 71% compared with 40% with surgery (832). In the Survival and Ventricular Enlargement (SAVE) trial, in which patients were treated with an ACE inhibitor after MI, even patients with mild MR experienced a worse prognosis than those without MR (833).

Severe MR may be due to infarction of the posterior papillary muscle, and in such instances, the area of infarction tends to be less extensive than in those patients in whom the MR is due to severe LV dysfunction. Consequently, LV function may also be better preserved in these patients. The presence of pulmonary edema or cardiogenic shock in a patient with inferior STEMI should alert the physician to the possibility of acute MR and papillary muscle rupture (Figure 31). Diagnosis is made by transthoracic or transesophageal echocardiography. All patients with papillary muscle rupture should be considered for urgent surgery. The patient should be stabilized with an IABP, inotropic support, and afterload reduction (to reduce regurgitant volume and pulmonary congestion) while emergency surgery is arranged. Coronary angiography should also be undertaken before surgery. Although emergency mitral valve replacement is associated with a relatively high mortality rate (20%), overall mortality and ventricular function are improved compared with medical therapy alone. Delay in operation appears to increase the risk of further myocardial injury, other organ injury, and subsequent death (834). Most patients will require mitral valve replacement, although mitral valve repair has also been reported in selected circumstances. Five-year survival after surgery has been reported to be 60% to 70% (835-839).

Severe MR, in the absence of papillary muscle rupture, often indicates extensive infarction and severe LV dysfunction. These patients may present a much more difficult management problem, particularly if surgery is required. Initial management should include afterload reduction and possible IABP. In many cases, the MR will improve over the next several days with aggressive medical management. If surgery is required because of critical coronary anatomy or ongoing ischemia, an intraoperative transesophageal echo should be undertaken to assess the mitral valve. Mitral valve surgery, usually annuloplasty, should be undertaken at the same time as CABG for patients with ischemic MR greater than 2+ (840,841). Clearly, operative mortality is increased in such patients, particularly in the elderly, with a marked decrease in LV function.

7.6.7.3. 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. **Coronary artery bypass grafting should be undertaken at the same time as repair of the VSR. *(Level of Evidence: B)***

The frequency of acute rupture of the intraventricular septum (VSR) (Figure 31) appears to have declined in the reperfusion era. It is estimated to occur in fewer than 1% of patients with STEMI (GUSTO-I) (829,842). Whereas previous pathological and clinical studies indicated the mean time from MI to rupture as 3 to 5 days, data from the GUSTO-I trial and SHOCK registry indicate that the highest risk for development of a postinfarct VSR occurred within the first 24 hours after infarction in patients receiving fibrinolytic therapy (842,843). Although emergency surgical repair was formerly thought to be necessary only in patients with pulmonary edema or cardiogenic shock, it is now recognized as equally important in hemodynamically stable patients (844-846). Because all septal perforations are exposed to shear forces and necrotic tissue removal processes by macrophages, the rupture site can abruptly expand, resulting in sudden hemodynamic collapse even in patients who appear to be clinically stable with normal LV function (846). Insertion of an IABP and prompt surgical referral are recommended for almost every patient with an acute VSR. Invasive monitoring is recommended in all patients, together with judicious use of inotropes and a vasodilator to maintain optimal hemodynamics. Nitroprusside is often used because it provides afterload reduction and can be titrated intravenously. Surgical repair usually involves excision of all necrotic tissue and patch repair of the VSR, together with coronary artery grafting. Surgical mortality remains high and has been reported to be between 20% and 50% (842-845,847,848). Mortality is particularly high in patients with cardiogenic shock (844,849) and was reported to be 87% in the SHOCK registry. However, surgical mortality is significantly less than for medically treated patients. In GUSTO-I (842), the mortality rates for surgical or medically treated patients were 47% and 94%, respectively.

A limited number of patients with postinfarction VSR have been treated by transcatheter closure with a septal occluding device. Most of these cases have been managed several weeks after infarction or have had prior surgical intervention with a residual defect. At this time, surgical closure remains the procedure of choice, although percutaneous closure does offer some hope for the future (850).

7.6.7.4. 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)***

Cardiac rupture may account for recurrent pain and occurs in 1% to 6% of all patients admitted with STEMI (829,851-854) (Figure 31). 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. The frequency of cardiac rupture has 2 peaks: an early peak within 24 hours and a late one from 3 to 5 days after STEMI. Early rupture is related to the initial evolution of infarction before significant collagen deposition, and late rupture is related to expansion of the infarct-related ventricular wall (852,855). Cardiac rupture is observed most frequently in patients with their first MI, those with anterior infarction, the elderly, and women. Other risk factors include hypertension during the acute phase of STEMI, lack of previous angina and MI, lack of collateral blood flow, Q waves on the ECG, use of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs), and use of fibrinolytic therapy more than 14 hours after onset (854,855). Fibrinolytic therapy decreases risk of cardiac rupture (853,856). Although there is an increase in the risk of early rupture after late administration of fibrinolytic therapy (i.e., more than 14 hours), the overall incidence of rupture is reduced. The most important determinants in preventing rupture are successful early reperfusion and the presence of collateral circulation (852,853). Pseudoaneurysm is a serious complication after rupture of the free wall. Clot forms in the pericardial space, and an aneurysmal wall containing clot and pericardium prevents exsanguination. Prompt surgical correction is always indicated for pseudoaneurysm to prevent rupture.

Pericardiocentesis for relief of tamponade and emergency surgical repair may be lifesaving (857,858). Ideally, the pericardium in this case should be opened surgically or tapped in the operating room. Echocardiography is valuable in the diagnosis of free-wall rupture and pseudoaneurysm, but for relief of tamponade in this setting, rapid fluid replacement is essential. Ideally, the patient should be in the operating room as soon as possible and fully prepared for cardiopulmonary bypass to prevent hemodynamic collapse. In these circumstances, delay to perform coronary angiography is inadvisable (859).

Surgery includes repair of the ventricle with a direct suture technique or patch to cover the ventricular perforation (857), in addition to CABG as needed. Alternatively, the use of cyanoacrylate glue has been described to hold the patch in place over necrotic myocardium (860). Most series of patients reaching the operating room for management of this complication are small, with the surgical mortality rate in these patients being up to 60% (859,861).

7.6.7.5. 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)*

Ventricular aneurysm after STEMI usually occurs on the anterior aspect of the LV in association with total LAD occlusion and a wide area of infarction. Clinical consequences include angina pectoris, CHF, thromboembolism, and ventricular arrhythmias. Patients with STEMI who receive fibrinolytic therapy and exhibit a patent infarct-related artery have a significantly reduced incidence of LV aneurysm formation compared with those who do not (7.2% versus 18.8%) (862). The need for surgery for ventricular aneurysm early after STEMI is rare, but it may be necessary for control of heart failure or intractable ventricular arrhythmias unresponsive to conventional therapy (863). Surgical techniques include plication, excision with linear repair, and ventricular reconstruction with endoventricular patches to maintain better physiological function (863-865). The adequacy of the residual LV in terms of size and function is a critical determinant on prognosis. Current mortality rates are reported to be 3.3% to 7.2% (863,864). Patients with severe LV dysfunction have an increase in mortality that has been reported to be as high as 19% for an ejection fraction less than 0.20 (866). Operative survivors have clear improvement in New York Heart Association class and a 60% 5-year survival rate (867).

7.6.7.6. Mechanical Support of the Failing Heart

7.6.7.6.1. 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. *(Level of Evidence: B)***
2. **Intra-aortic balloon counterpulsation is recommended for STEMI patients with low-output state. See Section 7.6.3. *(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. *(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. *(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. *(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. *(Level of Evidence: C)*

The IABP improves diastolic coronary blood flow and reduces myocardial work. These physiological effects of the IABP are especially helpful in patients with STEMI with ongoing or recurrent ischemic discomfort, hypotension from ischemia-mediated LV dysfunction, and cardiogenic shock (see section 7.6.5). The IABP is a useful stabilizing measure for patients in whom cardiac catheterization and revascularization are being considered.

Selected patients with cardiogenic shock after STEMI, especially if not candidates for revascularization, may be considered for either a short- or long-term mechanical support device to serve as a bridge to recovery or to subsequent cardiac transplantation. Of the many devices available to support these patients (868), short-term devices include centrifugal pumps and LV assist devices (LVADs) (869). Extracorporeal membrane oxygenation (ECMO), a cardiopulmonary bypass system placed through either the femoral or intrathoracic vessels, serves patients with heart failure and concomitant respiratory failure. These systems are limited by their short-term usefulness of less than 1 week and by problems with bleeding and thrombosis. Some consider ECMO a poor method of support because it does not decompress the LV (869). Patients who are subsequently determined to be transplant candidates may also be converted to a bridge-to-transplant device, thus creating a bridge to a bridge. About 10% of all patients treated with LVADs have them inserted for hemodynamic support after STEMI. This application has not been widely used because of the many comorbidities encountered in such patients, many of whom die before surgery. Experience with LVADs implanted in selected patients within 14 days after infarction has shown a survival rate of 74% to transplantation or explantation (870). This experience suggests that ventricular assist device implantation for cardiogenic shock after STEMI may reduce the mortality currently associated with medical management. The use of assist devices has been extensively reviewed in a separate ACC consensus conference report (868).

7.6.7.7. Cardiac Transplantation After STEMI

Cardiac transplantation has been reported for patients who have sustained irreversible acute myocardial injury associated with cardiogenic shock (871-873). Most patients so transplanted have been initially treated with an LVAD as a bridge to recovery or transplantation. Many such patients, however, do not meet criteria for transplantation because of advanced

age and extensive comorbidity. With appropriate case selection, satisfactory results can be obtained. Of 25 patients with post-STEMI cardiogenic shock and a mean age of 48 years, 3 died while on devices and 18 (72%) survived transplantation (873).

7.7. Arrhythmias After STEMI

Cardiac arrhythmias are common in patients with STEMI and occur most frequently early after development of symptoms. The mechanisms for ventricular tachyarrhythmias include loss of transmembrane resting potential, reentrant mechanisms due to dispersion of refractoriness in the border zones between infarcted and nonischemic tissues (874), and the development of foci of enhanced automaticity. Reperfusion arrhythmias, more commonly seen in the post-fibrinolytic era, appear to involve washout of toxic metabolites and of various ions such as lactate and potassium (875). Atrial arrhythmias have as additional causes excessive sympathetic stimulation, increased atrial stretch due to ventricular failure or AV valvular insufficiency, proarrhythmic effects of pericarditis, and atrial infarction. Bradyarrhythmias may be due to overstimulation of vagal afferent receptors and resulting cholinergic stimulation, as well as to ischemic injury of conducting tissues. The treatment of cardiac arrhythmias is based on the presumptive mechanism, the ongoing hemodynamic consequences, and, whenever possible, the results of clinical studies.

7.7.1. Ventricular Arrhythmias

7.7.1.1. Ventricular Fibrillation

Class I

Ventricular fibrillation 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 electric 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)*

Disturbances of cardiac rhythm are common during STEMI. Early-phase arrhythmias are probably largely a result of microreentry. Although other electrophysiological mechanisms such as enhanced automaticity and triggered activity have been proposed in experimental models of STEMI, convincing evidence for their role in human STEMI is not yet established (876). Important contributory factors include heightened adrenergic nervous system tone, hypokalemia, hypomagnesemia, intracellular hypercalcemia, acidosis, free fatty acid production from lipolysis, and free radical production from reperfusion of ischemic myocardium (876-878). The relative importance of each of these factors in the pathogenesis of arrhythmias during STEMI has not been established, nor has it been clearly shown that aggressive measures specifically targeted at 1 or more of these mechanisms can be relied on clinically to reduce arrhythmia frequency in STEMI.

Primary VF should be distinguished from secondary VF, the latter occurring in the presence of severe CHF or cardiogenic shock (879). Late VF develops more than 48 hours after onset of STEMI. Ventricular fibrillation is more common in the elderly (greater than 75 years of age) (880). The incidence of primary VF is highest (around 3% to 5%) in the first 4 hours after STEMI and declines markedly thereafter (881). Some epidemiological data suggest that the incidence of primary VF in STEMI may be decreasing in the current era, possibly owing to aggressive attempts at infarct-size reduction, correction of electrolyte deficits, and a greater use of beta-adrenoceptor–blocking agents (882). Additional epidemiological data from the Worcester Heart Attack Study more convincingly demonstrate that the case-fatality rate of primary VF has declined over time (883). Contrary to prior belief, primary VF appears to be associated with significantly higher in-hospital mortality, but those persons who survive to hospital discharge, particularly if primary VF occurred within the first 4 hours after STEMI, have the same long-term prognosis as patients who do not experience primary VF (884).

Primary VF remains an important contributor to risk of mortality during the first 24 hours after STEMI. Therefore, a reliable method for its prediction and prevention remains desirable but has not been established despite extensive clinical investigation. Classification of ventricular arrhythmias in ascending order of risk of primary VF (warning arrhythmias) was proposed, but this approach lacks appropriate specificity and sensitivity (885-887).

Accelerated idioventricular rhythm occurs frequently during the first 12 hours of infarction. Data from the prereperfusion era do not support development of accelerated idioventricular rhythm as a risk factor for development of VF (886,888). In patients receiving fibrinolysis or undergoing primary PCI, accelerated idioventricular rhythm may be a

reperfusion arrhythmia and does not indicate an increased risk of VF (889). Thus, it is best managed by observation and should not trigger initiation of antiarrhythmic prophylaxis against VF.

A meta-analysis of randomized trials of prophylaxis with lidocaine has shown a relative reduction in the incidence of primary VF by about 33%, but this was offset by a trend toward increased mortality, probably from fatal episodes of bradycardia and asystole (890). The use of prophylactic lidocaine was assessed in patients with STEMI in the GUSTO-I and GUSTO-IIb trials (891). After adjustment for baseline imbalances, the odds of death were not significantly different with or without lidocaine. Thus, even though it is less clear that lidocaine causes harm, there is no convincing evidence that its prophylactic use reduces mortality, and the prior practice of routine (prophylactic) administration of lidocaine to all patients with known or suspected STEMI has been largely abandoned.

Routine administration of intravenous beta-adrenoceptor blockers to patients without hemodynamic or electrical (AV block) contraindications is associated with a reduction in incidence of early VF (892). In the absence of contraindications (see Section 6.3.1.5), it is reasonable to initiate beta-blockade intravenously, followed by an oral regimen. Suitable regimens include intravenous metoprolol at 5 mg every 2 minutes for 3 doses, if tolerated, followed by 50 mg orally twice per day for at least 24 hours and then increased to 100 mg twice per day. An alternative regimen is atenolol 5 to 10 mg IV followed by 100 mg orally on a daily basis.

Clinical experience and observational data from CCU populations have identified hypokalemia as an arrhythmogenic risk factor for VF (877,878). Low serum levels of magnesium have not been clearly shown to be associated with an increased risk of VF (878), although tissue depletion of magnesium remains a potential risk factor. Although randomized clinical trial data do not exist to confirm the benefits of repletion of potassium and magnesium deficits in preventing VF, it is sound clinical practice to maintain serum potassium levels at greater than 4.0 mEq/L and magnesium levels at greater than 2.0 mEq/L in patients with acute MI.

Ventricular fibrillation should be treated with an unsynchronized electric shock using an initial monophasic shock energy of 200 J. If this is unsuccessful, a second shock using 200 to 300 J and, if necessary, a third shock using 360 J is indicated (893). The appearance of biphasic waveform defibrillators has led to some confusion regarding the comparability of biphasic to monophasic defibrillating energies. Overall, the energy requirement for equivalent biphasic therapeutic effect is about one half of the energy requirement for a monophasic discharge. Given the rapid evolution of resuscitation methodology, clinicians should follow the most current ACLS protocol (629). For example, for patients with VF not easily converted by defibrillation, vasopressin 40 U IV push may be substituted for epinephrine 1 mg. Randomized trials have addressed the use of intravenous amiodarone versus placebo and versus lidocaine for patients with out-of-hospital cardiac arrest. Although this population is somewhat different from the CCU population with primary VF, many patients with out-of-hospital VF have STEMI as the precipitating cause (894). These randomized trials have shown that the use of intravenous amiodarone is superior to placebo (895) and to lidocaine (896) in survival to hospital admission for patients with shock-resistant VF or VT. Neither trial, however, demonstrated improved survival to hospital discharge. In contrast, small studies comparing lidocaine to bretylium failed to show significant differences in the proportion of patients surviving to hospital admission (897,898); the use of procainamide in cardiac arrest is based on a small, 20-patient study (899). The use of lidocaine to treat VF refractory to electric shock or pulseless VT followed by unsynchronized electric shock has not been demonstrated to be beneficial in this setting and has been labeled "class indeterminate" by the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (900).

There are no firm data to help define an optimal management strategy for prevention of recurrent VF in patients who have sustained an initial episode of VF in the setting of STEMI. It seems prudent to correct any electrolyte and acid-base disturbances and to administer beta-adrenoceptor–blocking agents to inhibit increased sympathetic nervous system tone and prevent ischemia (876). The clinical trials of amiodarone cited above studied bolus administration of amiodarone only during the arrest setting. Thus, in the absence of arrhythmia recurrence, antiarrhythmic drugs should not be maintained beyond a 6- to 24-hour period. They should then be discontinued so that the patient's ongoing need for antiarrhythmic treatment can be reassessed.

7.7.1.2. 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 of 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 car-**

diac 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 bpm 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, and 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)*

Several definitions have been used for VT in the setting of STEMI. Nonsustained VT lasts less than 30 seconds, whereas sustained VT lasts more than 30 seconds and/or causes earlier hemodynamic compromise that requires immediate intervention. On the basis of ECG appearance, VT has also been categorized as monomorphic or polymorphic. Although short bursts (fewer than 5 beats) of nonsustained VT of either monomorphic or polymorphic configuration may be seen frequently, contemporary epidemiological data do not suggest that they are associated with a sufficiently increased risk of sustained VT or VF to warrant prophylactic therapy.

The vast majority of episodes of VT and VF after STEMI occur within the first 48 hours (881). Traditionally, sustained VT or VF that occurs outside of this time frame is thought to deserve especially careful evaluation, including consideration of electrophysiology (EP) studies. In addition, monomorphic VT at rates less than 170 bpm is unusual as an arrhythmia early after STEMI and suggests a more chronic (mature) arrhythmogenic substrate (515,901-903). VT that occurs more than 48 hours after STEMI may denote an arrhythmic substrate deserving of further evaluation by an EP study.

MANAGEMENT STRATEGIES FOR VT. Cardioversion is always indicated for episodes of sustained, hemodynamically compromising VT (876). In the absence of clinical evidence of effective perfusion, urgent electrical conversion of VT is indicated. Rapid, polymorphic-appearing VT should be considered similar to VF and managed with an unsynchronized discharge of 200 J, whereas monomorphic VT with rates greater than 150 bpm can usually be treated with a 100-J synchronized discharge (893). Immediate cardioversion is generally not needed for rates below 150 bpm unless hemodynamic compromise is present.

Episodes of sustained VT that are somewhat better tolerated hemodynamically may initially be treated with drug regimens including amiodarone or procainamide. Unfortunately, the data supporting the use of any specific antiarrhythmic therapy in this setting are scant. Although the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiac Care differentiate between patients with normal and impaired LV function, impairment of LV function is likely in the STEMI setting. Thus, recommendations for patients with STEMI parallel the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiac Care for patients with impaired LV function and place the use of amiodarone above that of other antiarrhythmics (900). Indeed, amiodarone has produced favorable data in cardiac arrest, and in long-term randomized trials, it is associated with a reduction in arrhythmic death and a small reduction in overall mortality (904). Knowledge of the pharmacokinetics of antiarrhythmic agents in patients with STEMI is important because dosing varies considerably, depending on age, weight, and hepatic and renal function.

Rare episodes of drug-refractory sustained polymorphic VT (electrical storm) have been reported in cases of STEMI. Anecdotal evidence suggests that these episodes may be related to uncontrolled ischemia and increased sympathetic tone and are best treated by intravenous beta-adrenoceptor blockade (905), intravenous amiodarone (906), left stellate ganglion blockade (907), IABP, or emergency revascularization. Intravenous amiodarone and/or intravenous magnesium may also be used.

Nonsustained VT is not a common cause of hemodynamic compromise and consequently does not require acute therapy (Figure 10) (223). Nonetheless, it is an important arrhythmia that may denote a high-risk arrhythmic substrate. Indeed, when it occurs more than 4 days after STEMI in patients with a depressed ejection fraction, it may be a harbinger of future risk of sudden death (908). In unusual cases, although the VT is nonsustained, the rate may be so rapid as to reduce cerebral perfusion sufficiently to cause symptoms (i.e., nonsustained VT at a rate of 200 bpm for 10 seconds). In those cases, pharmacotherapy similar to that recommended for sustained VT may be instituted.

7.7.1.3. 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)*

Before the present era of care of the STEMI patient with antiplatelet therapy, beta-blockade, ACE inhibitors, and, above all, reperfusion strategies, it was thought that ventricular warning arrhythmias preceded VF. Careful monitoring has refuted this concept, and treatment of these rhythm disturbances is not recommended unless they lead to hemodynamic compromise. All post-STEMI patients with ventricular arrhythmias should undergo assessment of electrolyte levels (especially potassium and magnesium) and have other metabolic parameters (i.e., arterial pH) assessed.

The effect on survival of the pharmacological suppression of ventricular premature beats after MI was assessed in the Cardiac Arrhythmia Suppression Trial (909). Patients receiving class I antiarrhythmic drugs for suppression of ventricular premature beats did more poorly than the placebo-treated patients. Therefore, suppression of ventricular premature beats with class I antiarrhythmic drugs is not a goal of post-STEMI therapy.

7.7.1.4. 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)***

Accelerated idioventricular rhythms are characterized by a wide QRS complex, with a regular rate higher than the atrial rate and lower than 100 bpm. The appearance of an idioventricular rhythm is an inexact indicator of reperfusion. Treatment of idioventricular rhythm is not indicated, and suppression of the rhythm may lead to hemodynamic compromise.

Accelerated junctional rhythms are characterized by a regular narrow QRS not preceded by atrial activity, with rates above 60 bpm. This rhythm may indicate digitalis intoxication and is more often seen in inferior STEMI than in anterior STEMI. In general, treatment of accelerated junctional rhythm is not indicated.

7.7.1.5. Implantable Cardioverter Defibrillator Implantation in Patients After STEMI

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. **An ICD is indicated for patients without spontaneous VF or sustained VT more than 48 hours after STEMI whose STEMI occurred at least 1 month previously, who have an LVEF between 0.31 and 0.40, demonstrate additional evidence of electrical instability (e.g., nonsustained VT), and have inducible VF or sustained VT on EP testing. *(Level of Evidence: B)***

Class IIa

If there is reduced LVEF (0.30 or less) at least 1 month post-STEMI and 3 months after coronary artery revascularization, it is reasonable to implant an ICD in post-STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI. *(Level of Evidence: B)*

Class IIb

1. **The usefulness of an ICD is not well established in STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI who have a reduced LVEF (0.31 to 0.40) at least 1 month after STEMI but who have no additional evidence of electrical instability (e.g., nonsustained VT). *(Level of Evidence: B)***
2. **The usefulness of an ICD is not well established in STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI who have a reduced LVEF (0.31 to 0.40) at least 1 month after STEMI and additional evidence of electrical instability (e.g., nonsustained VT) but who do not have inducible VF or sustained VT on EP testing. *(Level of Evidence: B)***

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)*

In general, VF or hemodynamically significant sustained VT taking place more than 2 days after STEMI in the absence of recurrent MI or potentially reversible ischemia indicates electrical instability and portends a poor prognosis (910,911). There are only 3 randomized trials (AVID [Antiarrhythmics Versus Implantable Defibrillators], CASH (Cardiac Arrest Study Hamburg), and CIDS [Canadian Implantable Defibrillator Study]) that compare the ICD with antiarrhythmic therapy in this patient population (912-914). Although the focus of these studies was not specifically the patient with prior or recent STEMI, the populations, as expected, all had a high prevalence of coronary disease and prior MI (Table 26) (912-914).

Only the AVID study showed a benefit of ICD therapy on mortality. However, the meta-analysis by Connolly et al. (914) clearly demonstrated the similarity of the trials and the

Table 26. Clinical Trials of Secondary Prevention of Sudden Death in ICDs: Applicability to the Post-MI Population

Study	AVID (912)	CASH (913)	CIDS (914)
Patients	1016	191	659
Prior MI, %	61	51	77
LVEF	0.32 ± 0.13	0.45 ± 0.18	0.34 ± 0.14
Presenting arrhythmia: VF or VT, %	100	100	86

ICD = implantable cardioverter defibrillator; MI = myocardial infarction; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

consistency of overall results for patients with prior MI. The summary hazard ratio was 0.72 (95% CI 0.60 to 0.87; p equals 0.0006) for total mortality and 0.50 (95% CI 0.37 to 0.67; p less than 0.0001) for arrhythmic death. Thus, patients with VF or hemodynamically significant sustained VT that takes place more than 2 to 3 days after STEMI in the absence of recurrent MI or other readily reversible cause should receive an ICD (Table 27) (915-918).

The management of nonsustained VT in patients with prior MI has proven more challenging. In the presence of LV dysfunction, this arrhythmia is associated with a 2-year mortality estimated at 30% (919,920), of which approximately 50% is believed to be arrhythmic in origin. Subsequent studies suggest that this degree of risk occurs principally in patients with inducible sustained VT not treated with an ICD (921). Three large randomized trials have been performed to study primary prevention of sudden death in these patients. However, because these trials were purposely not designed as post-STEMI trials, a conservative interpretation requires knowledge of when patients were randomized in relationship to their last previous known MI.

In the first prospective randomized trial completed in such a patient population, improved survival was documented after implantation of ICDs in patients with nonsustained VT and EP study–inducible and nonsuppressible ventricular tachyarrhythmias compared with conventional drug therapy, including amiodarone (915). Patients could not be randomized until at least 3 weeks after MI. Results of another prospective randomized trial, the Multicenter Unsustained Tachycardia Trial (MUSTT), showed reduced mortality with aggressive therapy for patients with low ejection fraction (0.40 or less), nonsustained VT on Holter monitoring, and inducible sustained ventricular tachyarrhythmias at EP study (916). Most of this benefit appeared to be due to ICD placement (918). In MUSTT, patients could be randomized as early as 4 days after MI; however, only 16% of patients were enrolled within 1 month of MI, which limits conclusions regarding benefit in patients early after STEMI. The MADIT 2 (Multicenter Automatic Defibrillator Implantation Trial 2) study enrolled 1232 post-MI patients with an LVEF of 0.30 or less. Patients were randomized to ICD therapy or not without the requirement for EP screening for inducible ventricular tachyarrhythmia (917). At a mean follow-up of 20 months, mortality was 14.2% in individuals who had ICDs and 19.8% in the conventionally treated group, a 5.6% absolute and 31% relative risk reduction for death. Of potential importance for management of patients recovering from STEMI, ICD therapy was not implemented until at least 1 month after MI and 3 months after coronary artery revascularization (Figure 32).

Thus, evidence from the randomized trials conclusively supports the concept that for patients with coronary disease, LV dysfunction, and high risk of life-threatening ventricular arrhythmias, ICD therapy is more effective than antiarrhythmic therapy. Indeed, an important contribution of the randomized clinical trials has been to refine the estimated contribution of risk factors for arrhythmic death or cardiac arrest in patients with coronary disease and LV dysfunction. For example, in the MUSTT database, each 5% decrease in LVEF from 0.40 to 0.20 conferred a 19% incremental relative risk of arrhythmic death or cardiac arrest. Inducibility at EP study increased risk by 63%. These simple risk factors, therefore, allow the clinician to select those patients most likely to benefit from ICD therapy in the late post-STEMI phase (922). The published studies, however, do not systematically address management considerations within the first month after STEMI. MADIT enrolled patients at least 3 weeks after MI, MUSTT at least 4 days, and MADIT 2 at least 1 month. Nonetheless, there is conceptual uniformity of the results of all 3 trials to support ICD therapy for patients at high risk of sudden cardiac death after STEMI.

Although the ejection fraction criteria used to define a degree of LV dysfunction severe enough to confer high risk are not uniform from study to study, a reduced ejection fraction remains the critical measurement to determine whether a post-STEMI patient is at high risk for late ventricular arrhythmia. Furthermore, ejection fraction is not always stable after STEMI. In a cohort of 252 patients who had sustained an anterior wall STEMI, 53% had at least a 5-point increase in ejection fraction at 90 days, whereas only 16% had a drop of at least 5 points (923). Thus, ejection fraction should be measured at least 1 month after STEMI before a decision regarding ICD placement is made. Finally, the variability of ejection fraction measured by different techniques (924) should also be taken into account by the clinician caring for the patient.

If there is reduced EF (0.30 or less) at least 1 month after STEMI and 3 months after coronary artery revascularization, it is reasonable to implant an ICD without a preceding diagnostic EP study. If the patient has an EF between 0.31 and 0.40, additional evidence of electrical instability should be sought to help with management decisions. If markers of electrical instability are detected on noninvasive testing (nonsustained on monitoring), an EP study is the next diagnostic

Table 27. Clinical Trials of Prevention of Sudden Death in ICDs: Applicability to the Post-MI Population

Study Name (Reference)	Year	Patients, n	Days After MI	Qualifying Arrhythmia	EF Upper Limit, mean	EPS	Mortality Hazard ICD vs no ICD (95%CI)
MADIT (915)	1996	196	More than 20	3-30 VPBs; rate greater than 120 bpm	35%, 26%	Yes†	0.46 (0.26-0.82)
MUSTT (916)	1999	704	More than 3*	Greater than 2 VPS; rate greater than 100 bpm	40%, 30%	Yes‡	0.42 (0.28-0.62)§ (918)
MADIT-2 (917)	2002	1232	More than 29	None necessary	30%, 23%	No	0.69 (0.51-0.93)

ICD = implantable cardioverter defibrillator; MI = myocardial infarction; EP = electrophysiological; EF = ejection fraction; EPS = EP study; CI = confidence interval; VPB = ventricular premature beat; VPS = ventricular premature stimulus. [Change to EP study per Dawn]
*Only 16% of the overall MUSTT population was randomized within 1 month of MI.
†Randomized MADIT patients had inducible VT not suppressed by a procainamide infusion during EP study.
‡Randomized MUSTT patients had inducible VT and were randomized to antiarrhythmic drug therapy. On the basis of clinical indications, some patients received ICDs during the course of follow-up.
§This hazard ratio compares MUSTT patients in the antiarrhythmic arm who received ICDs with those who received only EP-guided antiarrhythmic therapy.

step. If inducible VF or sustained VT is found at EP study, an ICD is indicated. The Writing Committee endorses additional research on noninvasive markers of electrical instability and the results of EP testing to help clarify management of decisions in such patients (see Section 7.11). The usefulness of an ICD is less well established for patients in whom no inducible VF or sustained VT is detected at EP study. As shown in Figure 32, such patients do not receive an ICD but should receive medical therapy (post-STEMI) as discussed in this guideline. An ICD is not indicated in patients with STEMI who do not experience spontaneous VF or sustained VT more than 48 hours after STEMI and in whom the ejection fraction is greater than 0.40 at least 1 month after STEMI.

Unfortunately, published clinical trials have not addressed the patient with a low ejection fraction within the first month after STEMI, which is thought to be a particularly high-risk period. Preliminary findings from DINAMIT (Defibrillator in Acute Myocardial Infarction Trial), a clinical trial of ICD versus conventional therapy in patients 6 to 40 days after MI with ejection fraction less than 0.35 and evidence of impaired autonomic tone, showed a reduction in arrhythmic mortality at the cost of an increase in nonarrhythmic mortality, yielding no net benefit of an ICD implanted in the first month after STEMI (Connelly S; oral presentation, American College of Cardiology 53rd Annual Scientific Session, March 2004, New Orleans, LA). Given this gap in knowledge, the ongoing Home Automatic External Defibrillator Trial is testing the hypothesis that provision of an AED to patients with anterior STEMI for home use will improve survival beyond that achieved from the typical lay response to sudden cardiac arrest (135). Additionally, wearable external defibrillators have been developed that may be applicable for high-risk patients after STEMI (926).

7.7.2. Supraventricular Arrhythmia/AF

Class I

1. **Sustained AF and atrial flutter in patients with hemodynamic compromise should be treated with one or more of the following:**
   a. **Synchronized cardioversion with an initial monophasic shock of 200 J for AF and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. *(Level of Evidence: C)***
   b. **For episodes of AF 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 (927). *(Level of Evidence: C)***
      ii. **Intravenous digoxin for rate control, principally for patients with severe LV dysfunction and heart failure. *(Level of Evidence: C)***

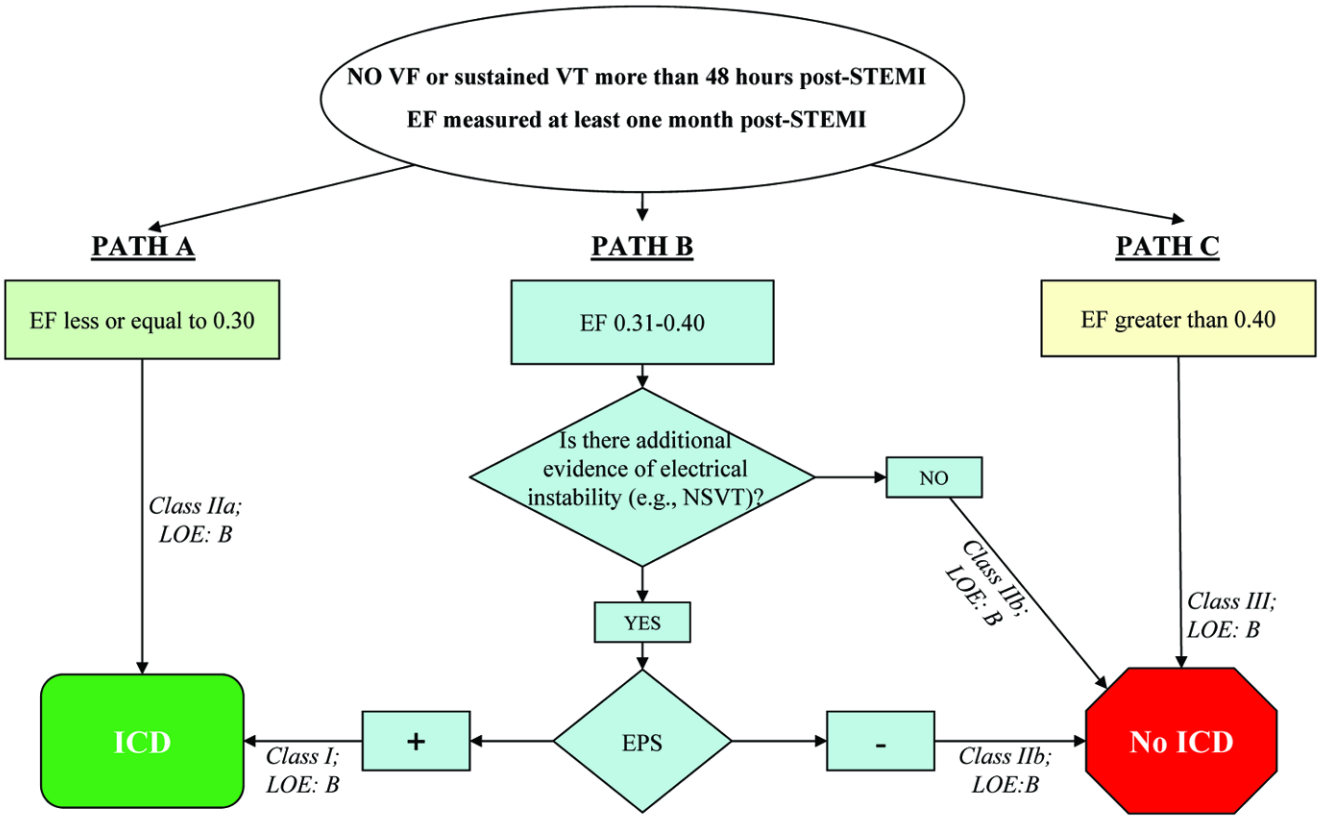

Figure 32. An evidence-based algorithm for primary prevention of sudden death in post-STEMI patients without spontaneous VF or sustained VT at least 1 month post-STEMI to aid in selection of implantable cardioverter/defibrillator (ICD) in patients with STEMI and diminished ejection fraction (EF). The appropriate management path is selected based upon left ventricular ejection fraction (LVEF) measured at least one month after STEMI. These criteria, that are based on the published data, form the basis for the full-text guidelines in section 7.7.1.5. All patients, whether an ICD is implanted or not, should receive medical therapy as outlined in the full-text guidelines. VF = ventricular fibrillation; VT = ventricular tachycardia; STEMI = ST-elevation myocardial infarction; NSVT = nonsustained VT; LOE = level of evidence; EPS = electrophysiological study; LVEF = left ventricular EF.

2. **Sustained AF 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 AF and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. *(Level of Evidence: C)***
3. **For episodes of sustained AF or flutter without hemodynamic compromise or ischemia, rate control is indicated. In addition, patients with sustained AF or flutter should be given therapy with anticoagulants. Consideration should be given to conversion of sinus rhythm in patients without a history of atrial fibrillation or flutter prior to STEMI. *(Level of Evidence: C)***
4. **Re-entrant 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)*

Atrial fibrillation occurs more frequently than atrial flutter or paroxysmal supraventricular tachycardia in patients with STEMI. The consequences and acute treatment of all 3

arrhythmias may be considered together, recognizing that in atrial flutter and supraventricular tachycardia, atrial pacing may be effective in terminating the tachycardia (928-933). Estimates of the incidence of AF in patients with STEMI vary depending on the population sampled. In the CCP, 22% of Medicare patients aged 65 years or older who were hospitalized for STEMI had AF (934). In the Trandolapril Cardiac Evaluation (TRACE) study of patients with LV dysfunction associated with STEMI, 21% had AF (935). Among the causes of AF in the immediate post-STEMI setting are excessive sympathetic stimulation, atrial stretch due to LV or RV dysfunction, atrial infarction due to circumflex or right coronary lesions, pericarditis, hypokalemia, underlying chronic lung disease, and hypoxia (807,929,936-940). Thus, AF occurs more often in patients with larger infarcts or anterior location of reinfarction and in those whose hospital course is complicated by CHF, complex ventricular arrhythmias, advanced AV block, atrial infarction, or pericarditis. Atrial fibrillation may also occur in patients with inferior STEMI secondary to proximal right coronary artery occlusion with compromise of flow in the sinoatrial nodal artery, the major blood supply to the atria. In some studies, the incidence of AF after STEMI is decreased in patients receiving fibrinolytic therapy (929,941), whereas in other studies, the incidence is similar (942). In the GUSTO trial, patients treated with accelerated alteplase and intravenous UFH had a significantly lower incidence of AF and atrial flutter than patients treated with other fibrinolytic therapies (25). Systemic embolization is more frequent in patients with paroxysmal AF (1.7%) than in those without (0.6%), with half of the embolic events occurring on the first day of hospitalization and more than 90% occurring by the fourth day (943). Because AF can be associated with pericarditis, the development of PR-segment displacement on serial ECGs may predict risk of developing AF during hospitalization (941).

The development of AF is associated with a worse in-hospital and long-term prognosis. In a study of 106 780 elderly (Medicare) patients with AF during MI, about half presented with AF and half developed AF during hospitalization (934). The presence of AF during hospitalization increased short- and long-term relative mortality by 20% and 34%, respectively (Table 28) (935,944-946). Patients who developed AF during hospitalization had a worse prognosis than those with AF on admission (934). Stroke rates are also increased in patients with MI and AF compared with those without AF (944). Outcomes appear to have improved in the fibrinolytic era for patients with AF and STEMI compared with experience between 1981 and 1983 (942), but a stroke rate of 3.1% in the setting of AF and STEMI (944) emphasizes the importance of this association even in the era of fibrinolysis.

When AF occurs, the clinician must consider and correct, if possible, the underlying causes. The initial clinical decision is whether to proceed immediately to electrical cardioversion if the patient is unstable with a rapid heart rate and hypotension, intractable heart failure, or ischemic pain. Cardioversion should be performed when the patient is under adequate general anesthesia or has received medication to pro-

Table 28. Clinical Significance of AF During STEMI as Reported in Modern Randomized Controlled Trials

TRIAL (Reference)	Incidence of AF, %	Predictors of Developing AF	Unadjusted Mortality Increase With AF	Adjusted Mortality Increase With AF
GUSTO-I (944)	7.9*	Increased age, CK, Killip class, heart rate	6.2% no AF vs. 14.3% with AF at 30 days	OR 1.4 (95% CI 1.3-1.5) at 30 days
TRACE (935)	21†	Female; increased age, LV dysfunction; anterior Q-wave MI	9% no AF vs. 18% with AF inhospital	OR 1.5 (95% CI 1.2-1.8) inhospital
GUSTO-III (945)	6.5*	Increased age, Killip class, hypotension, heart block, VF	6% no AF vs. 15% with AF at 30 days	OR 1.49 (95% CI 1.17-1.89) at 30 days
GISSI-3 (946)	7.8*	Increased age, heart rate, Killip class, hypertension	5% no AF vs. 12.6% with AF inhospital	OR 1.98 (95% CI 1.67-2.64)

AF = atrial fibrillation; STEMI = ST-elevation myocardial infarction; CK = creatine kinase; OR = odds ratio; CI = confidence interval.
*New AF after admission.
†All AF, including presentation with AF.

duce conscious sedation to avoid pain related to delivery of the electric shock. Short-acting anesthetic drugs or agents that produce conscious sedation are preferred because cardioversion patients should recover rapidly after the procedure (947).

Proper synchronization of the electric shock with the QRS complex calls for triggering by monitoring the R wave with an appropriately selected lead. In addition to R-wave amplitude, it is important that the monitored lead give a good view of P waves, thus facilitating assessment of the outcome of the procedure. The initial energy delivered with a monophasic waveform may be low (50 J) for cardioversion of atrial flutter. Higher monophasic shock energy is required for AF cardioversion, starting with at least 200 J. The monophasic shock energy output is increased successively in increments of 100 J until a maximum of 400 J is reached. Some physicians begin with higher energies to reduce the number of shocks (and thus the total energy) delivered (948). Energy settings should be reduced by about 50% of those noted above for monophasic shocks if a device that delivers a biphasic waveform is used. To avoid myocardial damage, the interval between 2 consecutive shocks should not be less than 1 minute (949). The optimal paddle position remains controversial; however, the electrodes should be in direct contact with the chest wall and not, for example, positioned over breast tissue. There is little experience with novel methods such as transvenous electrical cardioversion in patients with STEMI.

When medical therapy is selected, and in the absence of CHF or severe pulmonary disease, one of the most effective means of slowing the ventricular rate in AF is the use of intravenous beta-adrenoceptor–blocking agents such as 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). Heart rate, blood pressure, and the ECG should be monitored, and treatment should be halted when therapeutic efficacy is achieved or if systolic blood pressure falls below 100 mm Hg or there is excessive bradycardia (e.g., a heart rate below 50 bpm during treatment).

When there are absolute contraindications to beta-adrenergic blockade (bronchospastic lung disease or allergy), rate slowing may also be achieved by intravenous diltiazem (20 mg [0.25 mg/kg]) over 2 minutes followed by an infusion of 10 mg/h) or verapamil (2.5 to 10 mg IV over 2 minutes; may repeat a 5- to 10-mg dose after 15 to 30 minutes). There are concerns regarding the negative inotropic effects of these drugs and reports of increased post-STEMI mortality in patients with LV dysfunction taking long-term, short-acting oral diltiazem (950). Calcium antagonists, therefore, are not recommended for long-term rate control in post-STEMI patients; however, they may be useful for short-term rate control in hospitalized patients when beta-blockers are absolutely contraindicated.

Amiodarone has both sympatholytic and calcium antagonistic properties, depresses AV conduction, and is effective in controlling the ventricular rate in patients with AF. Intravenous amiodarone is effective and well tolerated in critically ill patients who develop rapid atrial tachyarrhythmias refractory to conventional treatment, but its effectiveness has not been evaluated sufficiently in patients with STEMI. In a small observational study of critically ill patients, there was a reduction in ventricular rate of 37 bpm after a 1-hour infusion of 242 mg of amiodarone (951). Amiodarone is considered a first-line agent for heart rate control in critically ill patients (951) and a second-line agent for those patients who are less hemodynamically unstable and can tolerate intravenous diltiazem. Amiodarone is the preferred agent to control repeat AF in patients with CHF or a low-output state.

Although intravenous digoxin may effectively slow the ventricular rate at rest, there is a delay of at least 60 minutes before onset of a therapeutic effect in most patients, and a peak effect does not develop for up to 6 hours. Digoxin is no more effective than placebo in converting AF to sinus rhythm (790,792,795) and may prolong the duration of AF (790,952). The efficacy of digoxin is reduced in states of high sympathetic tone, a common precipitant of paroxysmal AF. In a review of 139 episodes of paroxysmal AF recorded on Holter monitoring, there was no difference in the ventricular rates of patients taking digoxin and those not taking this medication (952). Other investigators, however, have found that digoxin reduces the frequency and severity of AF recurrence (953). Furthermore, the combination of digoxin and atenolol has been shown to be effective for ventricular rate control (954). Given the availability of more effective agents, digoxin is no longer first-line therapy for management of acute AF, but it plays a continuing role in patients with heart failure or LV dysfunction (955). Rapid administration of digoxin to achieve rate slowing may be accomplished by giving intravenous digoxin (8 to 15 mcg/kg [0.6 to 1.0 mg in a person weighing 70 kg]), with half the dose administered initially and the additional increment in 4 hours (956). This method provides a slower response than intravenous beta-adrenoceptor blockade or amiodarone; however, some effect on rate slowing may be detectable in 30 minutes to 2 hours.

Given that the databases reporting a marked increase in the risk of stroke in post-STEMI patients with AF do not report the time duration of AF at which stroke risk increases, it is unclear whether all post-STEMI patients with AF, even if transient, should receive anticoagulation or whether this aggressive posture should be reserved only for those with sustained AF of at least a few hours' duration. Indeed, the clinical circumstances, in particular whether there are other risk factors for post-STEMI stroke, should modulate the threshold for anticoagulation in the patient with transient AF.

When it has been determined that anticoagulation is required, either UFH or LMWH may be used. When UFH is selected, an intravenous bolus of 60 U/kg followed by a continuous intravenous infusion at 12 U/kg/h to maintain an aPTT of 50 to 70 seconds (approximately 1.5 to 2 times control) should be given. Alternatively, one of the LMWHs may be used at doses recommended by the manufacturer for full anticoagulation.

Once rate control has been accomplished, clinicians may opt to convert the patient to sinus rhythm to attain optimal hemodynamics and ultimately permit discontinuation of anticoagulants. Guidelines for electrical and chemical cardioversion for the stable patient with AF have been formulated (955). In patients with STEMI, special attention must be given to considerations of proarrhythmia with many commonly used antiarrhythmic agents. The preferred agent for intermediate or long-term use in the STEMI patient, based on the best safety record in post-MI trials, is amiodarone. Indeed, in a meta-analysis of 6553 randomized patients, 78% of whom were in post-MI trials, amiodarone resulted in a relative reduction in risk of death of 13%, which was wholly due to a greater reduction in arrhythmic death (914). The excess risk of pulmonary toxicity was only 1% per year. A post hoc analysis of GUSTO-III patients with AF also addressed the relative safety of other antiarrhythmic agents, including sotalol, in the post-STEMI setting. In a total of 317 patients with AF who received antiarrhythmic agents, no agent or class of agents was associated with increased mortality (957). However, the totality of evidence is much less compelling than for amiodarone after STEMI. Transient AF does not obligate the patient to receive long-term anticoagulation or antiarrhythmic agents, but if such treatment is elected, it is appropriate to limit their use to 6 weeks if sinus rhythm has been restored. In outpatients with paroxysmal AF, a controversy regarding the relative merits of rate control versus maintenance of sinus rhythm has been addressed by a large randomized clinical trial (958). AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) demonstrated no clear survival benefit for either strategy. However, patients with STEMI were not enrolled, and only 38.2% of the population had a prior diagnosis of coronary artery disease. Thus, the conclusions of AFFIRM should not be applied to the STEMI population, and the decision to continue chronic adjustable-dose oral anticoagulation indefinitely should be based on an overall assessment of the risk of thromboembolism in the individual patient.

7.7.3. Bradyarrhythmias

See Table 29 for recommendations. Sinus bradycardia occurs frequently, constituting 30% to 40% of AMI-associated cardiac arrhythmias. It is especially frequent within the first hour of inferior STEMI and with reperfusion of the right coronary artery (Bezold-Jarisch reflex) as a result of increased parasympathetic activity (vagal tone) (959). There are several other potential mechanisms, operating in isolation or in parallel, that account for the high incidence of sinus bradycardia. These include local increases in adenosine, local hyperkalemia, systemic metabolic derangements, and concomitant use of bradycardia-promoting medications (960).

Heart block may develop in approximately 6% to 14% of patients with STEMI. Intraventricular conduction delay has been reported in about 10% to 20% of patients with STEMI in past reviews (961). The development of AV and intraventricular blocks during STEMI is generally related to the extent of the ischemic/infarcted segment. As such, AV block predicts an increased risk of in-hospital mortality but is less predictive of long-term mortality in those who survive to hospital discharge (962-964). Nonetheless, in fibrinolysis trials, bundle-branch block was present on admission in only 4% but was predictive of a substantially increased in-hospital mortality rate (156). Indeed, the development of sudden AV block in the setting of anterior STEMI, once a feared complication, is quite unusual in the present CCU population in the postreperfusion era. Thus, the use of transvenous pacing has diminished, and the reliance on transcutaneous pacing has increased (Table 30) (965).

7.7.3.1. Acute Treatment of Conduction Disturbances and Bradyarrhythmias

Treatment of the conduction disturbances and resulting bradyarrhythmias can have either a prophylactic or therapeutic focus. The purpose of prophylactic pacing is to prevent symptomatic or catastrophic bradycardia by selecting and placing a transcutaneous or transvenous temporary pacemaker. Prophylactic pacing requires the clinician to predict which patients will develop sudden complete heart block with an inadequate ventricular escape mechanism. Fortunately, conduction disturbances generally occur in a stepwise fashion, so that knowledge of the specific ECG pattern can be used to estimate the risk of developing complete heart block and thus to guide the need for prophylactic temporary pacing. These estimates of risk, however, must be interpreted in the context of the risk of performing a procedure, particularly transvenous temporary pacing, on an unstable patient in the acute phase after STEMI, with all the attendant modern antithrombotic therapies increasing the risk of bleeding complications. Additionally, most of the clinically based algorithms to estimate risk of developing complete heart block were developed in the prefibrinolytic era, so they must be interpreted cautiously when applied to a modern post-STEMI population. In some cases, after the development of advanced AV block after STEMI, temporary transcutaneous or transvenous pacing must be used to maintain a stable cardiac rhythm and adequate hemodynamics. When the patient becomes pacemaker-dependent owing to a persistent conduction defect, however, temporary transvenous pacing is preferred compared with long-term transcutaneous pacing.

The pharmacological treatment of bradycardia and AV conduction disturbances during STEMI is a therapeutic, not prophylactic, measure. Pharmacotherapy centers on the use of atropine at doses of 0.6 to 1.0 mg IV repeated every 5 minutes until there is the desired effect or a total dose of 0.04 mg/kg (2 mg for a 50-kg person) has been reached. When there is infranodal block, however, atropine may increase the sinus rate without affecting infranodal conduction, and so the effective ratio of conduction may decrease, and the ventricular rate may decrease.

Other pharmacotherapies to treat bradyarrhythmias, such as isoproterenol and aminophylline, are not recommended because they are arrhythmogenic and increase myocardial oxygen demand. Glucagon has been used to treat bradycar-

Table 29. Recommendations for Treatment of Atrioventricular and Intraventricular Conduction Disturbances During ST-Elevation Myocardial Infarction

			First-Degree Block				Mobitz I Second-Degree AV Block				Mobitz II Second-Degree AV Block			
			Anterior MI		Nonanterior MI		Anterior MI		Nonanterior MI		Anterior MI		Nonanterior MI	
	Action	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**	**Action**	**Class**
Normal	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

Continued on next page

Table 29. *Continued*

This table is designed to summarize the atrioventricular (column headings) and intraventricular (row headings) conduction disturbances that may occur during acute anterior or nonanterior STEMI, the possible treatment options, and the indications for each possible therapeutic option.

AV = atrioventricular; MI = myocardial infarction; A = atropine; TC = transcutaneous pacing; TV = temporary transvenous pacing; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; RBBB = right bundle-branch block.

Action

There are 4 possible actions, or therapeutic options, listed and classified for each bradyarrhythmia or conduction problem:

1. Observe: continued ECG monitoring, no further action planned.
2. A, and A*: atropine administered at 0.6 to 1.0 mg IV 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, that at the discretion of the clinician, transcutaneous 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. The level of evidence for all cells and all treatments is B or C. 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–thrombolytic 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 prereperfusion era. There are no published randomized trials comparing different strategies of managing conduction disturbances after 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 intraventricular conduction disturbance, so look at row “New bundle-branch block.”
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.

dia caused by beta-blockers and calcium antagonists, although principally only when these agents have been used in toxic doses, particularly in combination (966).

The recommendations for prophylactic treatment of AV and intraventricular conduction blocks and the possible combinations are contained in Table 29.

7.7.3.1.1. 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)*

Ventricular asystole may be caused either by failure of the sinus node to generate a cardiac impulse or by the development of complete heart block. In either case, there is concurrent failure of the usual underlying escape mechanisms, whether atrial, junctional, or ventricular. Treatment of the acute event requires prompt institution of transcutaneous pacing, vasopressin, epinephrine, and atropine. It is important to address the underlying cause and discontinue medications that either suppress sinus node function, decrease AV nodal conduction, or suppress a potential escape mechanism. Cardiopulmonary resuscitation according to guidelines must be instituted (900). Transvenous pacing should be instituted unless the asystole is brief and a precipitating cause is found

Table 30. Features of AV Conduction Disturbances in Acute Myocardial Infarction

	Location of AV Conduction Disturbance	
Feature	**Proximal**	**Distal**
Site of block	Intranodal	Infranodal
Site of infarction	Inferoposterior	Anteroseptal
Compromised arterial supply	RCA (90%), LCx (10%)	Septal perforators of LAD
Pathogenesis	Ischemia, necrosis, hydropic cell swelling, excess parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
Predominant type of AV nodal block	First degree (pulse rate greater than 200 msec) Mobitz type I second degree	Mobitz type II second degree Third degree
Common promontory features of third-degree AV block	(a) First-second-degree AV block (b) Mobitz type I pattern	
Features of escape after third-degree block (a) Location (b) QRS width (c) Rate (d) Stability of escape rhythm	(a) Proximal conduction system (His bundle) (b) Less than 0.12 sec* (c) 45-60 per min but may be as low as 30 per min (d) Rate usually stable; asystole uncommon	(a) Distal conduction system (bundle branches) (b) Greater than 0.12 sec* (c) Often less than 30 per min (d) Rate often unstable with moderate to high risk of ventricular asystole
Duration of high-grade AV block	Usually transient (2-3 days)	Usually transient, but some form of AV conduction disturbances and/or intra-ventricular defect may persist
Associated mortality rate	Low unless associated with hypotension and/or CHF	High because of extensive infarction associated with power failure or ventricular arrhythmias
Pacemaker therapy (a) Temporary	(a) Rarely required; may be considered for bradycardia associated with LV power failure, syncope, or angina	(a) Indicated in patients with anteroseptal infarction and acute bifascicular block
(b) Permanent	(b) Almost never indicated because conduction defect is usually transient	(b) Indicated for patients with high-grade AV block with block in His-Purkinje systems and those with transient advanced AV block and associated bundle-branch block

AV = atrioventricular; RCA = right coronary artery; LCx = left circumflex artery; LAD = left anterior descending artery; sec = seconds; min = minutes; CHF = congestive heart failure; LV = left ventricular.

*Some studies suggest that a wide QRS escape rhythm (greater than 0.12 sec) after high-grade AV block in inferior infarction is associated with a worse prognosis.

Modified with permission from Antman EM. Cardiovascular Therapeutics: A Companion Guide to Braunwald's Heart Disease. 2nd ed. Philadelphia, PA: WB Saunders Co Ltd; 2001:273 (965).

(893,967,968). Vasopressin is an effective vasopressor and is as useful as epinephrine for the treatment of adult shock-refractory VF and pulseless electrical activity (969). In a study of patients with asystole out of the hospital, vasopressin use was associated with significantly higher rates of hospital admission (29.0% versus 20.3% in the epinephrine group; p equals 0.02) and hospital discharge (4.7% versus 1.5%, p equals 0.04). Among patients in whom spontaneous circulation was not restored with 2 injections of either vasopressin or epinephrine, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group but not in the epinephrine group (hospital admission rate 25.7% versus 16.4%; p equals 0.002; hospital discharge rate 6.2% versus 1.7%; p equals 0.002). Cerebral performance was similar in the 2 groups (969). Thus, in patients with STEMI with ventricular asystole, vasopressin (40 IU) would appear to be the preferable vasoconstrictor to administer first.

7.7.3.2. Use of Permanent Pacemakers

7.7.3.2.1. Permanent Pacing for Bradycardia or Conduction Blocks Associated With STEMI.

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 EP 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)***

Indications for permanent pacing after STEMI in patients experiencing AV block are related in large measure to the presence of intraventricular conduction defects (Table 29). Unlike some other indications for permanent pacing, the criteria for patients with STEMI and AV block do not necessarily depend on the presence of symptoms. Furthermore, the requirement for temporary pacing in STEMI does not by itself constitute an indication for permanent pacing (3).

The long-term prognosis for survivors of STEMI who have had AV block is related primarily to the extent of myocardial injury and the character of intraventricular conduction disturbances rather than the AV block itself (970-974). Patients with STEMI who have intraventricular conduction defects, with the exception of isolated left anterior fascicular block, have an unfavorable short- and long-term prognosis and an increased risk of sudden death (970,971,973,975). This unfavorable prognosis is not necessarily due to development of high-grade AV block, although the incidence of such block is higher in postinfarction patients with abnormal intraventricular conduction (971,976,977).

When AV or intraventricular conduction block complicates STEMI, the type of conduction disturbance, location of infarction, and relation of electrical disturbance to infarction must be considered if permanent pacing is contemplated. Even with data available, the decision is not always straightforward because the reported incidence and significance of various conduction disturbances vary widely (978). Despite the use of fibrinolytic therapy and primary PCI, which have decreased the incidence of AV block in STEMI, mortality remains high if AV block occurs (962,979-981).

Although more severe disturbances in conduction are generally associated with greater arrhythmic and nonarrhythmic mortality (971-974,976,978), the impact of pre-existing bundle-branch block on mortality after STEMI is controversial (978,982). A particularly ominous prognosis is associated with LBBB combined with advanced second- or third-degree AV block and with right bundle-branch block combined with left anterior or left posterior fascicular block (964,972,974,982) (Figure 33). Irrespective of whether the infarction is anterior or inferior, the development of an intraventricular conduction delay reflects extensive myocardial damage rather than an electrical problem in isolation (974). Although AV block that occurs during inferior STEMI can be associated with a favorable long-term clinical outcome, in-hospital survival is impaired, regardless of the use of temporary or permanent pacing in this situation (964,979,980,983). Furthermore, pacemakers should not be implanted if the peri-infarctional AV block is expected to resolve or to not have a negative effect on long-term prognosis, as in the case of inferior STEMI (981) with Mobitz I second-degree AV block.

With regard to sinus node dysfunction precipitated or unmasked by STEMI or associated necessary medical therapy, the indications for permanent pacing do not differ from the indications.

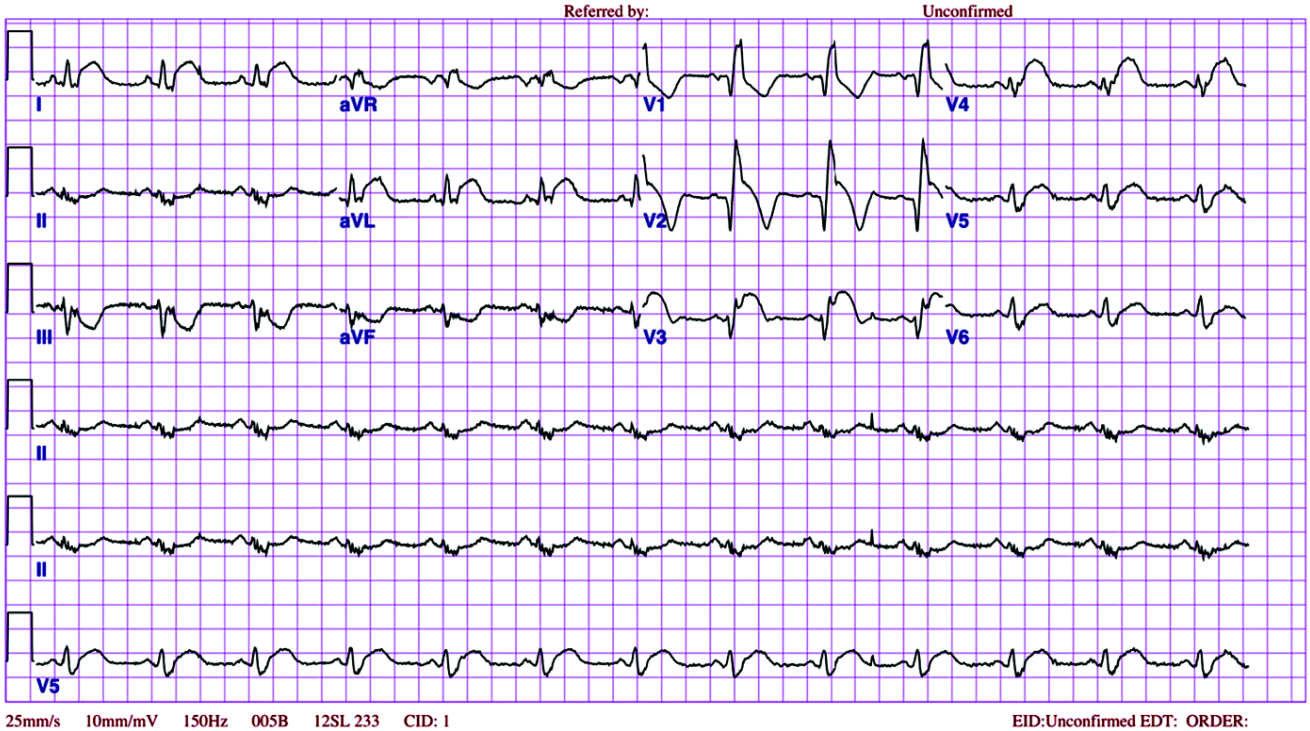

Figure 33. Twelve-lead ECG in a patient with anterior STEMI complicated by right bundle-branch block (RBBB) and left anterior fascicular block. Note the convex upward ST-elevation in V_2-V_3 consistent with anterior STEMI RBBB; the anticipated r-wave of the conventional rsR' pattern of RBBB has been replaced by a Q wave in V_1-V_2 as a result of anterior STEMI. The initial 80-ms forces of the QRS in the frontal plane are deviated to the left as a result of left anterior fascicular block. ECG = electrocardiogram; STEMI = ST-elevation myocardial infarction.

7.7.3.2.2. 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 (2 mg) doses of atropine have been used, transcutaneous or transvenous (preferably atrial) temporary pacing should be instituted. *(Level of Evidence: C)*

Sinus node dysfunction may be unmasked or caused by MI owing to disruption in the blood supply to the sinoatrial node, or owing to the use of medications such as beta-adrenergic blocking agents or calcium antagonists. The overall recommendations, indications, and levels of evidence are not different in non-MI and patients with STEMI, except that transient sinus bradycardia often occurs in the setting of inferior wall infarction, and treatment should avoid permanent pacing whenever possible. Thus, the published ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (984) should be used to guide therapy in patients with STEMI with persistent sinus node dysfunction. These guidelines should be applied with the proviso that new sinus node dysfunction that has first appeared during STEMI may be reversible, and when clinically possible, the decision to implant a permanent pacemaker should be delayed several days.

7.7.3.2.3. 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 AF or atrial 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)***

With regard to permanent pacing mode, there are no randomized trials that specifically address pacing mode selection (dual-chamber versus single-chamber ventricular pacing, with or without rate modulation) in patients with STEMI. In general, patients who need permanent pacing systems and are in sinus rhythm should receive a permanent dual-chamber pacemaker. In contrast, patients who have permanent AF or atrial flutter should receive a ventricular-pacing system. In post-STEMI patients with frequent episodes of paroxysmal AF or a persistent episode for which eventual

cardioversion is planned, the clinician must judge the likelihood of the patient being in sinus rhythm chronically before selecting a permanent dual-chamber or ventricular device. The data from randomized trials of pacing mode selection, although admittedly not obtained in a post-STEMI population, suggest specific programming features and goals to improve, or at least not further impair, LV function due to forced ventricular desynchronization by RV pacing. The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial in ICD patients without bradycardia but with LV dysfunction demonstrated that patients programmed to DDD at 70 bpm developed more heart failure than did patients programmed to VVI backup at a low rate (985). A post hoc analysis of the Mode Selection Trial (MOST) reported that in dual-chamber–paced patients with sinus node dysfunction and a median ejection fraction of 0.55, cumulative percent ventricular pacing above 40% was associated with an increase in heart failure hospitalizations. These emerging data suggest that when bradycardia pacing is instituted, the clinician might consider minimizing ventricular dyssynchrony through selection of devices and programming strategies to maintain low cumulative percent ventricular pacing (986). Whether the clinical application of these concepts will improve post-STEMI outcomes is unknown because these studies did not address the specific population on which these guidelines focus. Thus, the Committee has chosen not to incorporate these programming recommendations into the guidelines, pending the design and execution of more applicable prospective trials.

Nonetheless, when a permanent pacemaker is being considered for a post-STEMI patient, the clinician should address 2 additional questions regarding the patient: is there an indication for biventricular pacing, and is there an indication for ICD use? (986) Biventricular pacing has found a place in the treatment of advanced heart failure for patients with a low ejection fraction and a QRS duration greater than 130 ms (984). Patients with severe LV dysfunction may be eligible for implantation of an ICD for primary prevention of life-threatening ventricular arrhythmia, as well as bradycardia support. The algorithm to define whether an ICD is indicated is contained in Figure 32. See Section 7.7.1.5 for further discussion.

7.8. Recurrent Chest Pain After STEMI

The 2 most common cardiac causes of recurrent chest pain after STEMI are pericarditis and ischemia, the latter being the more common and potentially more serious. An ECG taken during the recurrent pain should be compared with ECGs from the index STEMI event (987). Usually, recurrent pain within the first 12 hours after onset of STEMI is considered to be related to the original infarction itself. Pericarditis is probably not responsible for significant chest discomfort in the first 24 hours.

7.8.1. Pericarditis

Class I

1. **Aspirin is recommended for treatment of pericarditis after STEMI. Doses as high as 650 mg orally (enteric-coated) 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 1 or more of the following:

a. **Colchicine 0.6 mg orally every 12 hours *(Level of Evidence: B)***
b. **Acetaminophen 500 mg orally every 6 hours. *(Level of Evidence: C)***

Class IIb

1. **Corticosteroids might be considered only as a last resort in patients with pericarditis refractory to aspirin or NSAIDs. 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)***
2. **Nonsteroidal anti-inflammatory drugs may be considered for pain relief; however, they should not be used for extended periods because of their effect on platelet function, an increased risk of myocardial scar thinning, and infarct expansion. *(Level of Evidence: B)***

Class III

Ibuprofen should not be used for pain relief because it blocks the antiplatelet effect of aspirin and it can cause myocardial scar thinning and infarct expansion. *(Level of Evidence: B)*

Pericarditis in STEMI occurs with extension of necrosis across the full thickness of the myocardial wall to the epicardium. Patients with pericarditis have larger infarcts, a lower ejection fraction, and a higher incidence of CHF (988,989). Pericarditis may appear up to several weeks after STEMI. Anterior chest discomfort mimicking ischemia can occur with pericarditis. However, pericardial pain usually has distinguishing characteristics, such as pleuritic and/or positional discomfort; radiation to the left shoulder, scapula, or trapezius muscle; and a pericardial rub, ECG J-point elevation with concave upward ST-segment elevation and PR depression. Detection of a 3-component rub is diagnostic of pericarditis. Pericardial effusion is evident echocardiographically in more than 40% of cases (990) but is rarely of hemodynamic consequence. A small effusion is not diagnostic of pericarditis because it can be demonstrated in the majority of patients with STEMI (991). On occasion, pericarditis may be a clinical clue to the presence of subacute myocardial rupture (see Section 7.6.7.4).

Focal pericarditis can be diagnosed electrocardiographically by either persistently positive T waves or reversal of initially inverted T waves during the first week after STEMI. However, similar T-wave alterations have also been observed when postinfarction pericardial effusion exists in the absence of clinically recognized pericarditis (992). Pericarditis is not associated with re-elevation of CK-MB. There are data to suggest its incidence has decreased in the reperfusion era (993-995). Interestingly, the Dressler syndrome (post-MI syndrome), an autoimmune-type carditis, has essentially disappeared (996) in the reperfusion era.

Neither the configuration of the ECG nor the absence or presence of the cardiac markers can absolutely establish a diagnosis of, or rule out, pericarditis. Jain described anterior ST-segment elevation secondary to acute pericarditis (997). Bonnefoy et al. studied 69 consecutive patients with idiopathic acute pericarditis (998). Cardiac troponin I was detected in 34 patients (49%), and the level of troponin was beyond the 1.5 ng/ml threshold in 15 (22%). Seven of these 15 patients underwent coronary angiography. All 7 patients had normal coronary angiograms. ST-segment elevation was found in 93% of the patients with troponin I greater than 1.5 ng/ml compared with 57% without troponin elevation (p less than 0.01). Patients with cardiac troponin I higher than 1.5 ng/ml were more likely to have had a recent infarction (66% versus 31%; p equals 0.01) and were younger (age 37 plus or minus 14 years versus 52 plus or minus 16 years; p equals 0.002).

Aspirin (162 to 325 mg/d) is the treatment of choice, but higher doses (650 mg every 4 to 6 hours) may be required (956,999). Nonsteroidal anti-inflammatory drugs may be considered for pain relief; however, they should not be used for extended periods because of their effect on platelet function, an increased risk of myocardial scar thinning, and infarct expansion. Corticosteroids, which are also efficacious for pain relief, are associated with scar thinning in the infarct zone and myocardial rupture (1000,1001). Therefore, corticosteroids should not be used except as a last resort. The risk-benefit ratio of continuing antithrombotic therapy in the presence of acute pericarditis always presents a clinical challenge. Usually such therapy can be continued safely but requires added vigilance for the detection of enlarging pericardial effusion or signs of hemodynamic instability. Any evidence of impending cardiac tamponade is an indication for prompt termination of antithrombotic therapy.

If NSAIDs are used, misoprostol, 200 mcg every 6 hours, should be used for gastric and renal protection (1002-1004). On the basis of the proven efficacy of colchicine therapy for familial Mediterranean fever, several small studies showed that colchicine could successfully treat or prevent the recurrence of acute pericarditis after conventional therapy, including corticosteroid therapy, had failed (1005). Colchicine may be administered at 0.6 mg every 12 hours, with or without a loading dose (1006-1008).

7.8.2. 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 less than 60 minutes from the onset of recurrent discomfort) implemented. *(Level of Evidence: C)*

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)*

It is important to differentiate pain due to pericarditis from pain due to ischemia. The latter is more likely when the chest pain is similar to the initial ischemic-type chest discomfort, occurring at rest or with limited activity during hospitalization. This may or may not be associated with re-elevation of the CK-MB, ST-segment depression or elevation, or pseudonormalization of inverted T waves (T-wave inversion on baseline ECG becoming upright during ischemia) (990).

Reinfarction occurs in 4% to 5% of patients who have received fibrinolytic therapy and aspirin (25,43,851,1009,1010). Reinfarction is associated with re-elevation of biomarkers after the initial peak of the index infarction. Diagnosis of reinfarction within 18 hours after initiation of fibrinolytic therapy should be based on recurrence of severe ischemic-type chest discomfort that lasts at least 30 minutes, usually but not always accompanied by recurrent ST-segment elevation of at least 0.1 mV in at least 2 contiguous ECG leads and re-elevation of CK-MB to more than the upper limit of normal or increased by at least 50% over the previous value (37). Pathological findings of rein-

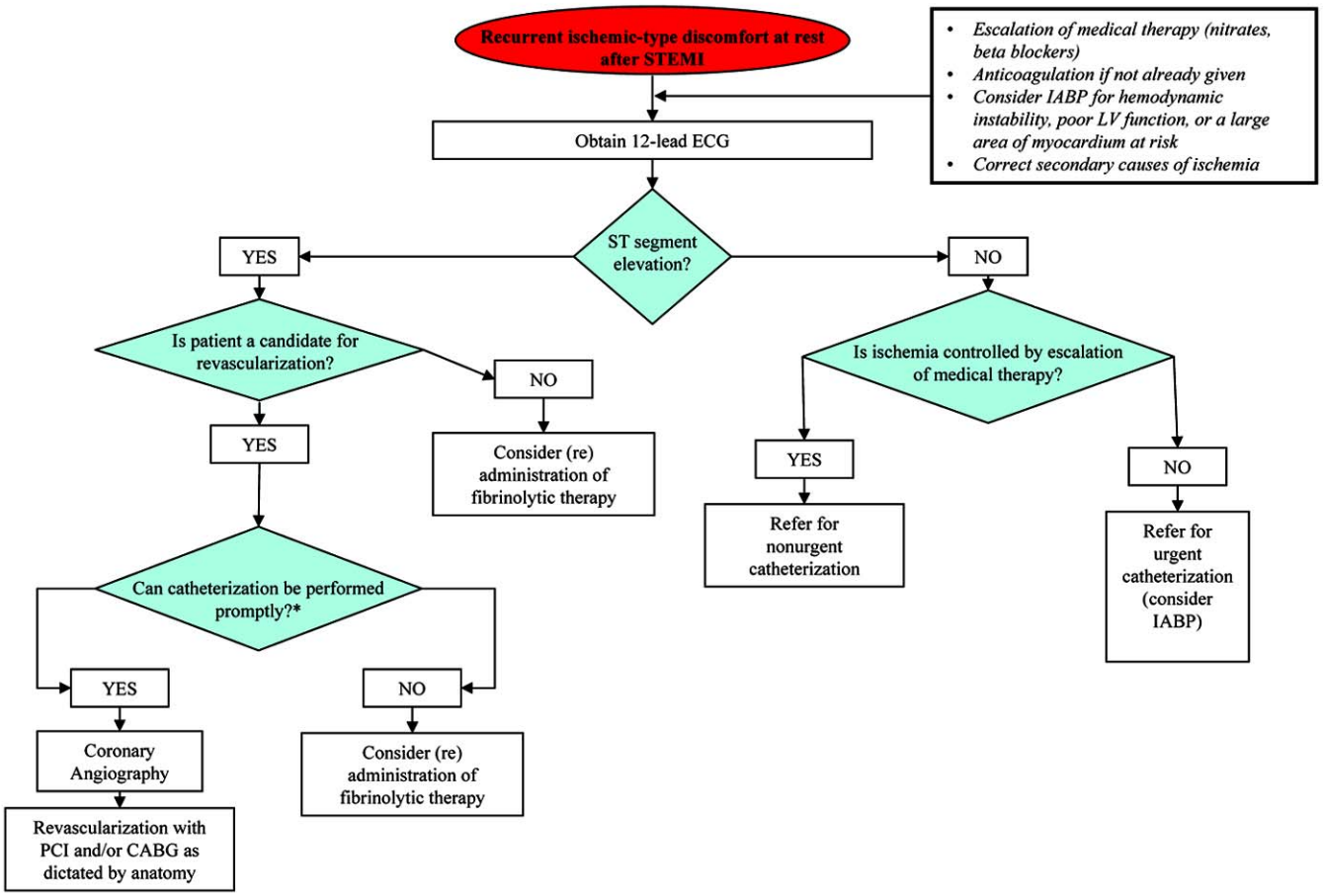

Figure 34. Algorithm for management of recurrent ischemia/infarction after ST-elevation myocardial infarction (STEMI). IABP = intra-aortic balloon pump; ECG = electrocardiogram; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery. *Ideally within 60 minutes from the onset of recurrent discomfort. Modified with permission from Braunwald et al. Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia, PA: WB Saunders; 2001:1196 (718).

farction show areas of healing myocardium along with the more recent necrosis, usually in the same vascular risk region of myocardial tissue perfused by the original infarct-related artery. Death, severe CHF, and arrhythmias are early complications of reinfarction, and there is an increased incidence of cardiogenic shock or cardiac arrest (25,43,1011). An algorithm for diagnosing reinfarction both early and late after fibrinolytic therapy is shown in Figure 12. In patients with recurrent MI after fibrinolysis, the mortality rate is increased up to 2 years; however, most of the deaths occur early (in the hospital), with little additional risk of death between the index hospitalization and 2 years later (512).

Patients with recurrent ischemic-type chest discomfort should undergo escalation of medical therapy, including beta-blockers (intravenously and then orally) and nitrates (sublingually and then intravenously); consideration should be given to initiation of intravenous anticoagulation if the patient is not already therapeutically anticoagulated. Secondary causes of recurrent ischemia, such as poorly controlled heart failure, anemia, and arrhythmias, should be corrected (Figure 34) (1012).

With recurrent suspected ischemic-type chest discomfort, coronary arteriography often clarifies the cause of chest discomfort with demonstration of a high-grade coronary obstruction. For patients who are considered candidates for revascularization, prompt reperfusion with PCI or CABG is indicated as dictated by the coronary anatomy (Figure 34) (509,515,1012). For patients who are not considered candidates for revascularization or for whom coronary angiography and PCI cannot be implemented rapidly (ideally in less than 60 minutes), readministration of fibrinolytic therapy is reasonable.

Another cause of chest discomfort to consider in patients recovering from STEMI is infarct expansion. This is characterized by nonspecific repolarization of abnormalities on the ECG, worsening hemodynamics, but no re-elevation of cardiac biomarkers (43). Management of infarct expansion should focus on diuresis and inhibition of the renin-angiotensin-aldosterone system (see Section 7.4.3).

7.9. Other Complications

7.9.1. Ischemic Stroke

Class I

1. **Neurological consultation should be obtained in STEMI patients who have an acute ischemic stroke. *(Level of Evidence: C)***

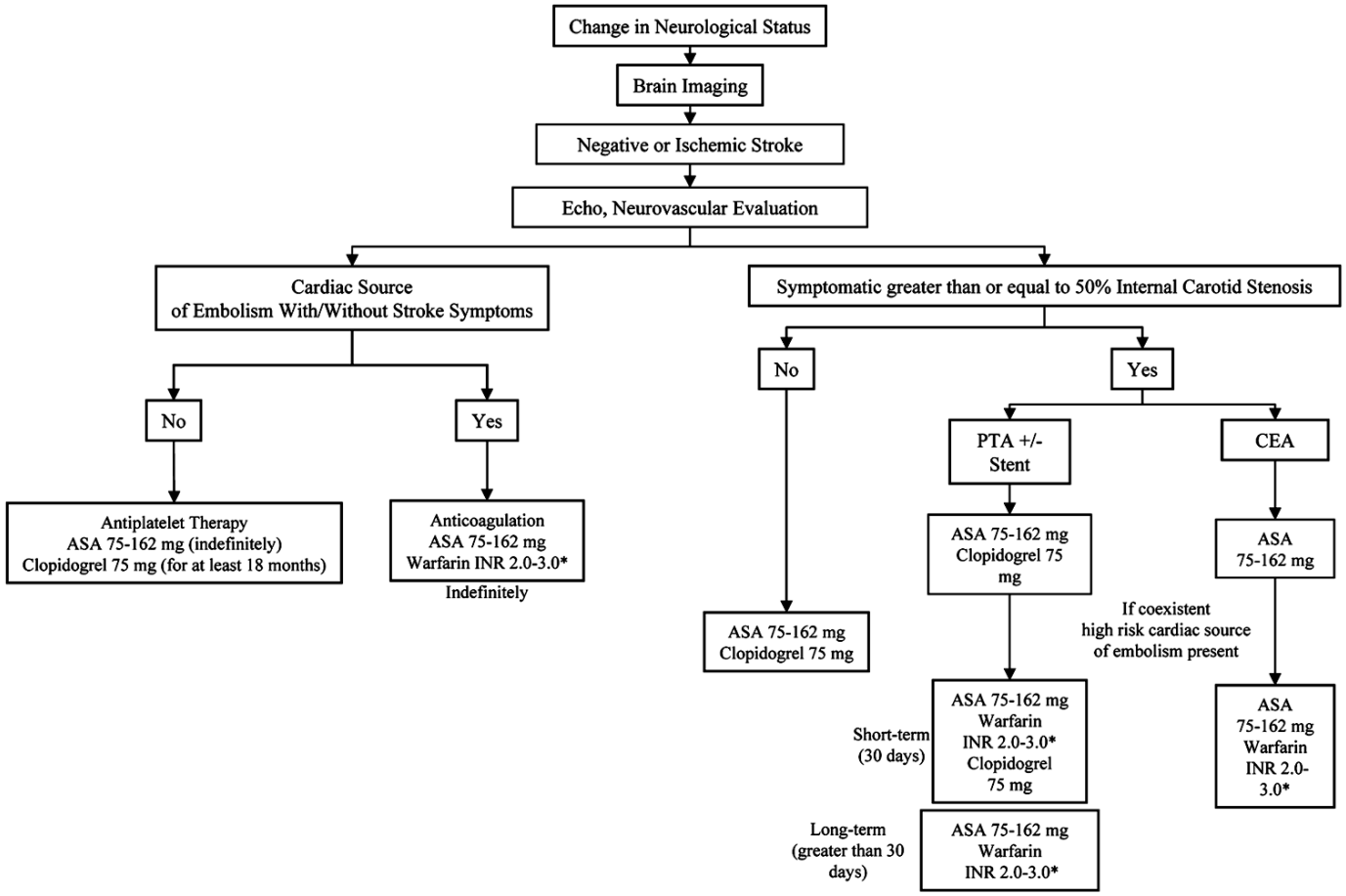

Figure 35. Algorithm for postreperfusion ischemic stroke treatment. Daily doses of antithrombotic therapy are shown in the algorithm. ASA = aspirin; INR = international normalized ratio; PTA = percutaneous transluminal angioplasty (carotid); CEA = carotid endarterectomy. *An INR of 2.0-3.0 is acceptable with tight control, but the lower end of the 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.

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 AF should receive lifelong moderate-intensity (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 (AF, mural thrombus, or akinetic segment) should receive moderate-intensity (INR 2 to 3) warfarin therapy in addition to aspirin (see Figure 35). 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 AF). 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)*

Acute stroke complicates 0.75% to 1.2% of MIs and is one of the most dreaded outcomes of STEMI (326,1013,1014). Although survival from STEMI has been increasing, mortality from post-STEMI stroke remains over 40% (1013). Prior stroke, hypertension, old age, decreased ejection fraction or multiple ulcerated plaques, and AF are the major risk factors for embolic stroke after STEMI (326,944,1015-1017). Anterior STEMI is often cited as a risk factor, but other infarct locations appear to have similar risk (1015,1018). AF

is by far the most important of these risk factors (1019). In the SAVE trial (1017), decreased ejection fraction (18% increased risk per every 5% decrease in ejection fraction) was independently associated with long-term stroke risk in patients with STEMI. Thrombus formation is promoted by extensive wall-motion abnormality, such as anteroapical akinesia or dyskinesia, and Killip class III or IV (1020). Embolic stroke after STEMI originates from LV thrombus or from the left atrium in the setting of AF and occurs even in patients treated with fibrinolysis (1015). It does not appear to be useful to test patients with STEMI, even with mural thrombus formation, for prothrombotic syndromes such as factor V Leiden mutation (1021). Several studies in patients with STEMI suggest that aggressive short- and long-term anticoagulation may reduce but not totally prevent mural thrombus formation (744,1022,1023) and occurrence of stroke (1024-1028). Most ischemic cerebral infarctions after fibrinolytic therapy for STEMI occur more than 48 hours after treatment (218,320,322,586). The highest-risk period is the first 28 days after STEMI (1014), but risk is elevated at least to 1 year. In GUSTO-I (1015), Mahaffey et al. found that the risk of ischemic stroke after coronary fibrinolysis may be predicted (1015). Prospective studies are needed to verify this observation. Compared with ICH, patients with ischemic cerebral infarction present more commonly with focal neurological deficits and less commonly with depressed level of consciousness; headache, vomiting, and coma are uncommon (360).

An algorithm for evaluation and antithrombotic therapy for ischemic stroke is shown in Figure 35. If the STEMI patient has sudden onset of a focal neurological deficit and the initial CT scan is negative for blood or mass effect, then ischemic cerebral dysfunction may be presumed in the absence of a severe metabolic disorder, seizures, autoimmune disease, or cancer. Neurological consultation is recommended to assist with planning the neurovascular evaluation and management issues. The location and nature of the ischemic brain lesion should be defined with repeat CT scan or magnetic resonance imaging scan. Vascular lesions should be evaluated with noninvasive techniques, such as carotid duplex sonography, transcranial Doppler, magnetic resonance angiography, CT angiography, or transesophageal echocardiography. For carotid territory symptoms and signs, evidence for a surgically important stenosis (greater than 50% linear diameter reduction on a catheter-based cerebral angiogram using the North American Symptomatic Carotid Endarterectomy Trial [NASCET] method) (1029) should clearly be sought.

The subacute to chronic pathophysiology of STEMI provides a rationale for clinicians to consider when choosing antithrombotic therapies for stroke prevention and treatment in this setting. A hypercoagulable state may exist for up to 6 months after STEMI (1030). This state may be accentuated by withdrawal of heparin and warfarin therapy (555).

In ISIS-2 (1031), use of aspirin was shown to reduce the occurrence of ischemic stroke. Thus, aspirin administration after STEMI, with or without ischemic cerebral infarction, is appropriate. However, for patients with ischemic cerebral infarction who undergo PCI and have no cardioembolic risk factors, the use of clopidogrel 75 mg/d (for at least 12 months) plus aspirin 75 to 162 mg/d (indefinitely) after STEMI is reasonable (578,728,1032). Patients with STEMI who have ischemic stroke but do not undergo PCI and do not have a cardiac source of embolism or surgically important carotid stenosis may be treated with aspirin/extended-release dipyridamole 25/200 mg plus aspirin 81 mg/d (1033).

A subgroup analysis from the CAPRIE trial (1032) in patients with a prior history of ischemic events suggested a benefit of clopidogrel (mean duration of treatment 1.6 years) over aspirin for the composite end point of ischemic stroke, MI, or vascular death (3.4% ARD, 95% CI 0.2 to 7.0; 14.9% RRR; p equals 0.045). Thus, for the STEMI patient who has an ischemic stroke without a documented cardiac source of embolism while on aspirin therapy, clopidogrel may be added for a period of 18 months.

Patients with cardiogenic sources of embolism, such as AF, LV mural thrombi, or akinetic segment of the LV myocardium, should receive moderate-intensity (INR 2 to 3) warfarin anticoagulation in combination with aspirin. The duration of moderate-intensity warfarin anticoagulation will vary according to the underlying strong source of cardiogenic embolism. Ischemic stroke patients with pre-existing or persistent AF require lifelong warfarin therapy (958), irrespective of 2-dimensional echocardiography findings. In general, patients with STEMI with LV mural thrombus should receive 3 months of warfarin therapy, a time believed to be sufficiently long for clot adherence and re-endothelialization to occur, leading to reduced embolic risk. However, if follow-up 2-dimensional echocardiography at 3 months in the STEMI patient with acute ischemic stroke shows findings that suggest an ongoing risk of cardiogenic embolism (e.g., new or enlarging mural thrombi or thrombi that are pedunculated or mobile), then long-term moderate-intensity warfarin anticoagulation is recommended.

If a surgically important internal carotid artery stenosis that explains the clinical findings is found, either carotid endarterectomy (1029,1034,1035) or carotid angioplasty with stenting and a distal protection device (1036,1037) (Yadav J; oral presentation, 2002 American Heart Association Annual Scientific Session, November 2002, Chicago, IL) could be performed. If surgical morbidity and mortality are acceptable, carotid endarterectomy may be performed 4 to 6 weeks after cerebral infarction. Preliminary data from 307 randomized patients in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial (Yadav J; oral presentation, 2002 American Heart Association Annual Scientific Session, November 2002, Chicago, IL) showed a significant reduction in the composite end point of 30-day death, STEMI/NSTEMI, or stroke in the stent arm compared with the endarterectomy arm (5.8% versus 12.6%, p equals 0.047). There was no difference in the occurrence of TIAs or major bleeding between the 2 groups, although the occurrence of cranial nerve injury was significantly higher in the

endarterectomy arm (0% versus 5.3%, p less than 0.01). One-year follow-up data are pending.

7.9.2. Deep Venous Thrombosis and Pulmonary Embolism

Class I

1. **Deep venous thrombosis 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 2-3. *(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)***

Prevention. Deep venous thrombosis and pulmonary embolism historically were relatively frequent complications of STEMI, but in the current era in which patients with STEMI almost universally receive anticoagulants, specific prophylaxis is seldom needed (1039). For patients with CHF after STEMI who are hospitalized for prolonged periods or unable to ambulate and who are not otherwise anticoagulated, the best evidence of safety and efficacy supports the use of low-dose LMWH (1040). Dosing depends on the specific LMWH chosen, and product-specific information should be consulted at the time of treatment.

Treatment. A high index of suspicion for DVT and pulmonary embolism is necessary, and patients suspected of having either condition should be evaluated immediately with an appropriate evidence-based diagnostic strategy (1041). Most patients with DVT or pulmonary embolism should be anticoagulated with LMWH. It is at least as effective as UFH in clinical trials, and a meta-analysis suggests it offers a lower total mortality (1042). Outside of carefully supervised clinical trials, LMWH is generally superior, because overshooting and undershooting the therapeutic range is commonplace with UFH in routine clinical practice. Low-molecular-weight heparin is less costly overall because it avoids intravenous administration and frequent laboratory testing. Dosing of LMWH depends on the specific product, and product-specific information should be consulted at the time of treatment. Warfarin should be initiated concurrently with LMWH, and LMWH should be continued until the INR reaches the therapeutic range of 2 to 3 (1041,1043). Warfarin should be continued for a duration specific to the individual patient's risk profile (1044). Patients with contraindications to anticoagulation with heparins will require alternative therapies, and some will require placement of an inferior vena cava filter. Detailed discussion of warfarin therapy duration, alternative anticoagulants, and vena cava filter placement criteria are beyond the scope of this guideline, and the reader should consult an evidence-based guideline on venous thromboembolic disease (1041,1043).

7.10. Coronary Artery Bypass Graft Surgery After STEMI

7.10.1. 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)*

There are no clear data regarding optimal timing of bypass surgery after STEMI (518,1045-1047). Most published studies are retrospective and observational in nature, with heterogenous patient cohorts and differences in inclusion criteria. Moreover, many patients undergoing emergency surgery tend to have comorbidities and risk factors, including decreased LV function, which are normally associated with an increase in operative mortality.

Coronary artery bypass grafting early after STEMI may carry substantial risk, particularly in unstable patients with Q-wave infarction and decreased LV function. Prior CABG, female gender, and advanced age compound this risk considerably (1045). Lee et al. (1048) reviewed 44 365 patients from New York State undergoing CABG. Mortality for those with or without a history of MI was 3.1% and 1.6%, respectively. Mortality was higher for patients with transmural infarction who underwent surgery within the first 24 hours (12.1% at less than 6 hours, 13.6% at 6 to 23 hours). At 2 weeks, mortality was 2.6%. Mortality for patients with non-transmural MIs was also elevated (11.5% at less than 6 hours, 6.2% at 6 to 23 hours) (Table 31) (1048). In another large series of 2296 patients undergoing CABG after MI, Creswell et al. reported mortality from surgery to be 9.1% at less than 6 hours after MI, 8.3% at 6 to 48 hours, 5.2% at 2 to 14 days, 6.5% at 2 to 6 weeks, and 2.9% at greater than 6 weeks. Urgency of surgery was the most important predictor of operative mortality (1049). When adjustments were made for the independent risk factors of urgency of operation, increased patient age, renal insufficiency, number of previous MIs, and hypertension, the timing between MI and CABG was not a significant predictor for death.

In reviewing 11 retrospective and prospective observational studies regarding CABG and MI, Crossman et al. (1046) concluded that timing of surgery after infarction was not necessarily an independent predictor of outcome. However, these studies did "appear to support an approach of medical stabilization for unstable patients post MI wherever possible

Table 31. Comparison of Hospital Mortality for CABG With Respect to Time of Operation: Transmural Versus Nontransmural MI

Time Since Operation	n*	Transmural MI Mortality, %	Nontransmural MI Mortality, %
Less than 6 hours	885	12.1	11.5
6-23 hours	556	13.6	6.2
1-7 days	7554	4.3	3.5
8-14 days	6712	2.4	2.7
Greater than or equal to 15 days	28 658	2.6	2.7

CABG = coronary artery bypass graft surgery; MI = myocardial infarction.
*Number of the 44 365 patients in the NY State Cardiac Surgery Registry who underwent CABG as the sole procedure from 1993-1996 and whose data were used in the analysis.
Modified from Lee et al. Ann Thorac Surg 2001;71:1197-202, Copyright © 2001, with permission from the Society of Thoracic Surgeons (1048).

to convert high risk emergency operations to lower risk more elective procedures" (1046). The Writing Committee believes that if stable patients with STEMI with preserved LV function require surgical revascularization, then CABG can be undertaken within several days of the infarction without an increased risk. In addition, surgery for patients who have mechanical complications of MI, such as VSR or papillary muscle rupture, or who have ongoing ischemia that has been unresponsive to other medical therapy and have vessels suitable for bypass, cannot usually be delayed. However, patients who have had a significant decrease in LV function as a result of STEMI and who are hemodynamically stable may benefit from a longer period of medical treatment to allow myocardial recovery to occur before surgical revascularization is undertaken. If a patient has critical coronary anatomy, such as greater than 75% left main coronary artery stenosis, then CABG should be undertaken during the same hospitalization. (See Section 3.2.2 of the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (518).)

7.10.2. Arterial Grafting

Class I

An internal mammary artery graft to a significantly stenosed LAD should be used whenever possible in patients undergoing CABG after STEMI. *(Level of Evidence: B)*

The routine use of the left internal mammary artery (IMA) for LAD grafting, with supplemental saphenous vein grafts to other coronary lesions, is generally accepted as the standard grafting method. A large, long-term follow-up study comparing patients receiving the left IMA-to-LAD and supplemental vein grafts to patients receiving saphenous vein grafts only demonstrated a significantly lower rate of recurrent angina and MI, a lower incidence of reoperation or PCI, and a higher actuarial 10-year survival among patients with IMA grafts (1050). Despite the clear advantage of the IMA graft, not all patients receive arterial grafts. In the PAMI-2 trial (522) of 120 patients undergoing surgery, only 31% received an IMA graft; no patients had cardiogenic shock at the time of surgery. On the other hand, Hirose et al. (1051) used arterial conduits in 96% of 47 patients undergoing emergency CABG within a mean of 27 hours from infarction, and operative mortality was 6.4%. In a further study, Hirotani et al. (1052) performed CABG on 68 patients within 30 days of infarction, with a mortality rate of 7.4%. CABG without arterial grafts was the sole predictor of an adverse survival. Although surgeons may be reluctant to use the IMA in patients after STEMI because of limited flow through the arterial graft and the time necessary to harvest it, the data suggest that IMA grafts can be used safely soon after STEMI with no increase in mortality; their use is associated with better long-term survival.

7.10.3. Coronary Artery Bypass Graft Surgery After Fibrinolytic Therapy

In the 3339 patients enrolled in the TIMI-II trial, CABG was performed as an emergency procedure (1.6%) or electively (10% during initial hospitalization), primarily for left main coronary stenosis or coronary anatomy not amenable to PCI and continuing, recurrent, or exercise-induced ischemia (1053). Of the 41 021 patients enrolled in the GUSTO-I trial, CABG was used in 8.6% at a mean of 8.5 days after fibrinolytic therapy (1054). Unstable patients undergoing CABG shortly after fibrinolytic therapy, primarily for continuing myocardial ischemia, have a higher operative mortality rate (13% to 17%) and increased use of blood products (1053,1055,1056) than hemodynamically stable patients operated on within 8 hours of fibrinolytic therapy, who have a relatively low (2.8%) mortality rate (1057). The only independent predictor of perioperative mortality in TIMI-II was performance of CABG within 24 hours of entry or PCI. The low 1-year mortality rate (2.2%) noted for operative survivors in this group may support the use of emergency operation for selected patients, however (1053). In the SHOCK trial (301), CABG was as successful as PCI in reducing mortality in patients with cardiogenic shock, although they had more complex coronary artery anatomy. The intraoperative use of aprotinin may reduce hemorrhage related to use of thrombolytic agents (1058).

7.10.4. Coronary Artery Bypass Graft Surgery 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)*

Coronary artery bypass graft surgery should be considered when recurrent ischemia occurs in patients with STEMI whose coronary artery anatomy is not suitable for PCI. Operative mortality in such patients is correlated closely with ejection fraction, and for patients with normal ejection fraction, it is nearly the same as that of elective CABG (1059-1061). The survival benefit for patients with reduced LV function supports the use of CABG in this situation.

7.10.5. Case Selection Concerns in CABG After STEMI

As cardiac surgical programs and individual surgeons come under scrutiny with regard to operative mortality rates, concern has been raised about the possibility that salvageable but high-risk patients may not be offered surgery. Omoigui et al. (1062) suggested that the reduction in mortality noted in New York State was caused by an outmigration of high-risk patients due to the increased scrutiny provoked by public release of mortality data. In a survey of New York State cardiac surgeons, Burack et al. (1063) reported that many surgeons refused to operate on at least 1 high-risk patient over the prior year, primarily because of public reporting. The Writing Committee believes strongly that patients should be offered surgical treatment if the treating team believes that the benefits outweigh the risks and that meaningful survival of the patient could result. Furthermore, appropriately validated risk-adjusted outcome measures should be used when evaluating the performance of an individual surgeon or surgical program. The ACC/AHA Guideline Update on Coronary Artery Bypass Graft Surgery has addressed the issue of institutional and individual surgical caseloads (518). Studies suggest that survival after CABG has improved over the last decade but is negatively affected when the surgery is performed in institutions that do fewer than a threshold of 200 cases per year. However, some institutions and practitioners maintain excellent outcomes despite relatively low volumes. In reviewing the outcome of 13 644 CABG procedures at 56 US hospitals, mortality was significantly lower at high-volume hospitals only for those patients considered as being at high or moderate risk (1064). Therefore, targeted transfer of high- to moderate-risk post-STEMI patients to high-volume institutions may be appropriate.

7.10.6. Elective CABG After STEMI in Patients With Angina

Class I

1. **Coronary artery bypass graft surgery is recommended for patients with stable angina who have significant left main coronary artery stenosis. *(Level of Evidence: A)***
2. **Coronary artery bypass graft surgery is recommended for patients with stable angina who have left main equivalent disease: significant (at least 70%) stenosis of the proximal LAD and proximal left circumflex artery. *(Level of Evidence: A)***
3. **Coronary artery bypass graft surgery 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. **Coronary artery bypass graft surgery is beneficial for patients with stable angina who have 1- or 2-vessel coronary disease without significant proximal LAD stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)***
5. **Coronary artery bypass graft surgery is recommended in patients with stable angina who have 2-vessel disease with significant proximal LAD stenosis and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)***

The role of surgical revascularization has been reviewed extensively in the ACC/AHA Guideline Update on Coronary Artery Bypass Graft Surgery (518). Consideration for revascularization after STEMI includes PCI and CABG. Providers should individualize patient management on the basis of clinical circumstances, available revascularization options, and patient preference. Elective CABG should improve survival relative to medical therapy in patients with MI who have 1) left main coronary artery stenosis; 2) left main equivalent (significant [at least 70%] stenosis of the proximal LAD and proximal left circumflex artery); 3) 3-vessel disease, particularly with decreased LV function; 4) 2-vessel disease with significant proximal LAD stenosis not amenable to PCI and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing; and 5) 1- or 2-vessel disease not amenable to PCI without proximal LAD stenosis but with a large area of viable myocardium at risk and high-risk criteria on noninvasive testing. The optimal timing of surgery has not been established. The risk is greatest within the first 48 hours of infarction and decreases over the next 2 weeks. Risk of operation is greatest for patients with decreased LV function, advanced age, female sex, renal failure, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, and previous CABG (1048,1061,1065).

7.10.7. Coronary Artery Bypass 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/d) 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)***

Aspirin therapy, particularly within the first 48 hours after CABG, appears to have significant benefits (1066,1067). Mangano et al. (1066) studied 5022 patients in a global registry who survived CABG. Aspirin therapy begun within 48 hours after surgery resulted in a 60% lower death rate at 30 days, as well as decreased rates of MI, stroke, renal failure, and bowel infarction. It is likely that these effects are mediated by both the anti-inflammatory and antithrombotic actions of aspirin (1067). Bleeding complications were also lower in the aspirin-treated group.

Patients with STEMI undergoing revascularization frequently receive 1 or more antiplatelet agents in addition to heparin, all of which may increase risk of serious bleeding during and after cardiac surgery. Because the mechanism and duration of action of the antiplatelet effects of aspirin, the ADP antagonists (ticlopidine and clopidogrel), and GP IIb/IIIa receptor antagonists (abciximab and eptifibatide) differ, the potential exists for an additive effect with a combination of these agents. In the CURE trial (728), in which 12 562 patients with unstable angina or NSTEMI were randomized to placebo plus aspirin or clopidogrel plus aspirin, there was an increased risk of major bleeding in the clopidogrel group (3.7%) compared with the placebo group (2.7%). Also, risk of bleeding was increased in patients undergoing CABG within the first 5 days of stopping clopidogrel. In a prospective study of 224 patients having CABG, Hongo et al. (1068) found reoperation for bleeding to be 10-fold higher in patients who had received clopidogrel within 7 days of surgery than in those who had received no clopidogrel. In the EPIC trial (Evaluation Prevention of Ischemic Complications; placebo or abciximab bolus or abciximab infusion) (1069), transfusion of red blood cells and platelets was significantly higher after treatment with abciximab.

Singh et al. (1070) found transfusion requirements to be higher for patients who underwent urgent CABG after having received abciximab during PCIs. In an analysis of 85 surgical patients in the EPILOG (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade) and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition in Stenting) trials, although platelet transfusions were higher in the abciximab groups, rates of major blood loss and transfusions of whole blood and packed red cells were the same in the abciximab and placebo groups (1071). Management strategies for patients who require surgery and subsequent treatment with antiplatelet agents will differ according to type of agent used and the urgency of surgery.

In many circumstances, it may not be feasible to delay surgery until platelet function has recovered. In patients treated with the small-molecule GP IIb/IIIa receptor antagonists, tirofiban and eptifibatide, platelet function returns toward normal within 4 hours of stopping treatment. Platelet aggregation does not return toward normal for more than 48 hours in patients treated with abciximab. Management strategies other than delaying surgery include platelet transfusions for patients who were recently treated with abciximab, reduced heparin dosing during cardiopulmonary bypass, and possible use of antifibrinolytic agents such as aprotinin or tranexamic acid (1072). Because clopidogrel, when added to aspirin, increases the risk of bleeding during major surgery, clopidogrel should be withheld for at least 5 days (728) and preferably for 7 days before surgery in patients who are scheduled for elective CABG (1073).

7.11. Convalescence, Discharge, and Post-MI Care

7.11.1. Risk Stratification at Hospital Discharge

Informal risk estimates are updated continually as the patient's clinical condition evolves and other information becomes available. For example, tests such as an echocardiogram may be obtained early during hospitalization to define an abnormal physical finding and thus provide data for risk stratification, even though they were not ordered for that purpose. Because patient preference is a critical determinant for any management pathway, it is difficult to produce a rigid algorithm for risk stratification.

There is, nevertheless, value in outlining general strategies for performing risk stratification testing, with an emphasis on avoiding redundancy. The most important immediate management decision is whether to refer a patient for cardiac catheterization. Patients who have not had catheterization as part of their initial treatment strategy should be evaluated for their risk of future cardiac events. Another major decision is referral for EP testing and possible placement of an ICD.

The risk stratification approach for decision making about catheterization is described in Figure 36. For patients who did not have an early catheterization and in whom revascularization therapy would be considered, the approach includes an early quantitative assessment of LVEF. Patients with an LVEF less than 0.40 should be considered for catheterization. For those with a higher LVEF, further stratification with stress testing is recommended. Various approaches are considered acceptable, including a submaximal stress test, a symptom-limited stress imaging test, or a pharmacological stress imaging test. Ambulatory ECG monitoring for ischemia after STEMI has significant limitations (e.g., resting ECG abnormal after infarction) and has not been incorporated into the algorithm in Figure 36 (71,1074). A symptom-limited stress test was not formerly recommended but is supported by data from DANAMI (515). The decision for referral to cardiac catheterization should then be based on the stress test results, with an indication related to the amount of ischemia quantified by test results. Patients with little or no ischemia may be better treated with medical therapy, a strategy supported by DANAMI.

The suggested algorithm for EP testing and ICD placement is shown in Figure 32. Electrophysiology testing is not indicated for patients with an LVEF less than 0.30 because they are presumed to benefit from an ICD, and an EP test is not necessary. Patients with VF after 48 hours, sustained VT, or hemodynamically significant VT are recommended for ICD placement without an EP test. For patients with an ejection fraction less than 0.40, an EP test is reserved those whose telemetry or Holter monitor show nonsustained VT.

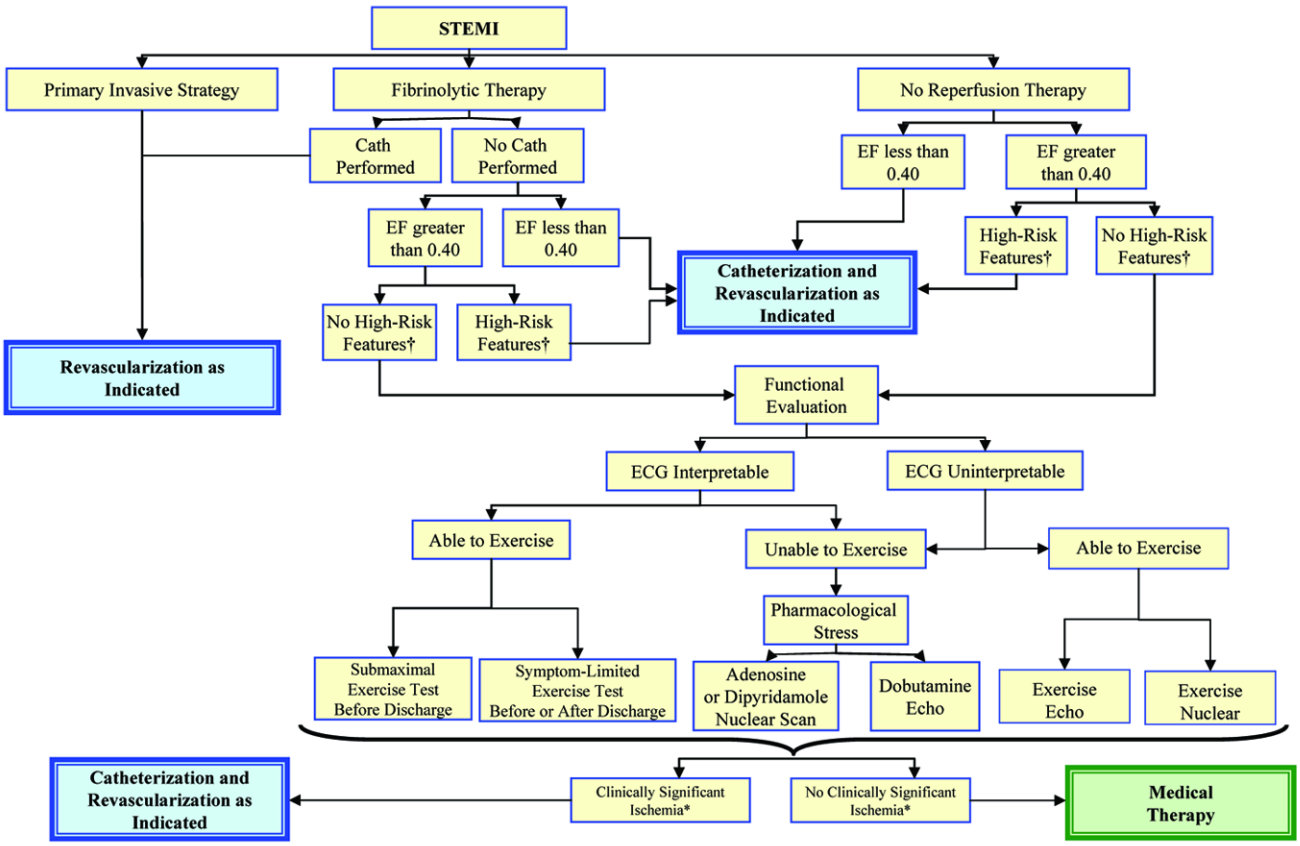

Figure 36. Evidence-based approach to need for catheterization (cath) and revascularization after ST-elevation myocardial infarction (STEMI). The algorithm shows treatment paths for patients who initially undergo a primary invasive strategy, receive fibrinolytic therapy, or do not undergo reperfusion therapy for STEMI. Patients who have not undergone a primary invasive strategy and have no high-risk features should undergo functional evaluation with 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 after STEMI. *Please see Table 23 of the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina for further definition (71). †Please see Table 3, Section 6.3.1.6.2 and Section 7.3 in the STEMI guideline for further discussion.

Physicians and their patients must make decisions about risk-reduction lifestyle and pharmacological approaches. At this point, however, all patients with STEMI are considered to be at sufficiently high risk to merit use of these secondary prevention interventions, including the use of cardiac rehabilitation, aspirin, appropriate lipid-lowering therapy, and beta-blockers (Table 32) (68).

There is a clear need for tools that can integrate comprehensive risk-stratification information in explicit estimates of absolute risks of cardiovascular outcomes with management decisions. Current risk stratification tests generally provide relative risk information, indicating average increases in risk, but their utility in guiding clinical decisions remains to be defined. The Writing Committee believes that further research in this area is necessary before making recommendations about the best use of these emerging risk stratification tools.

7.11.1.1. 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 post-discharge 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**

Table 32. Secondary Prevention for Patients With STEMI

Goals	Intervention Recommendations
Smoking:	Assess tobacco use. Strongly encourage patient and family to stop smoking and to avoid secondhand smoke.
Goal Complete cessation	Provide counseling, pharmacological therapy (including nicotine replacement and bupropion), and formal smoking cessation programs as appropriate. (See Section 7.12.4 in the full-text guidelines for further discussion.)
Blood pressure control:	*If blood pressure is 120/80 mm Hg or greater:*
Goal Less than 140/90 mm Hg or less than 130/80 mm Hg if chronic kidney disease or diabetes	• Initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients. *If blood pressure is 140/90 mm Hg or greater or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes:* • Add blood pressure–reducing medications, emphasizing the use of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system. (See Sections 7.12.6, 7.12.7, and 7.12.8.)
Lipid management: (TG less than 200 mg/dL)	Start dietary therapy in all patients (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol). Promote physical activity and weight management. Encourage increased consumption of omega-3 fatty acids.
Primary goal: LDL-C substantially less than 100 mg/dL	Assess fasting lipid profile in all patients, preferably within 24 hours of STEMI. Add drug therapy according to the following guide. (See Section 7.12.2.) LDL-C less than 100 mg/dL (baseline or on treatment): • Statins should be used to lower LDL-C. LDL-C greater than or equal to 100 mg/dL (baseline or on treatment): • Intensify LDL-C–lowering therapy with drug treatment, giving preference to statins.
Lipid management: (TG 200 mg/dL or greater)	If TGs are greater than or equal to 150 mg/dL or HDL-C is less than 40 mg/dL: • Emphasize weight management and physical activity. Advise smoking cessation.
Primary goal Non–HDL-C* substantially less than 130 mg/dL	If TG is 200-499 mg/dL: • After LDL-C–lowering therapy,† consider adding fibrate or niacin.‡ If TG is greater than or equal to 500 mg/dL: • Consider fibrate or niacin‡ before LDL-C–lowering therapy.† • Consider omega-3 fatty acids as adjunct for high TG. (See Section 7.12.2.)
Physical activity: Minimum goal 30 minutes 3 to 4 days per week Optimal daily	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 minutes of activity, preferably daily but at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work). Cardiac rehabilitation programs 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. (See Sections 7.12.12 and 8.2.)

Continued on next page

Table 32. *Continued*

Goals	Intervention Recommendations
Weight management: Goal BMI 18.5-24.9 kg/m^2	Calculate BMI and measure waist circumference as part of evaluation. Monitor response of BMI and waist circumference to therapy. Start weight management and physical activity as appropriate. Desirable BMI range is 18.5-24.9 kg/m^2.
Waist circumference: Women: less than 35 in Men: less than 40 in	If waist circumference is greater than or equal to 35 inches in women or greater than or equal to 40 inches in men, initiate lifestyle changes and treatment strategies for metabolic syndrome. (See Section 7.12.3.)
Diabetes management: Goal HbA1C less than 7%	Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA_{1c}. Treatment of other risk factors (e.g., physical activity, weight management, blood pressure, and cholesterol management). (See Section 7.12.9.)
Antiplatelet agents/ anticoagulants	Start and continue indefinitely aspirin 75 to 162 mg/d if not contraindicated. Consider clopidogrel 75 mg/d or warfarin if aspirin is contraindicated. Manage warfarin to INR 2.5 to 3.5 in post-STEMI patients when clinically indicated or for those not able to take aspirin or clopidogrel. (See Sections 7.12.5 and 7.12.11 and Figure 37 for further details of antiplatelet and anticoagulant therapy at hospital discharge.)
Renin-angiotensin-aldosterone system blockers	ACE inhibitors in all patients indefinitely; start early in stable high-risk patients (anterior MI, previous MI, Killip class greater than or equal to II [S_3 gallop, rales, radiographic CHF], LVEF less than 0.40). Angiotensin receptor blockers in patients who are intolerant of ACE inhibitors and with either clinical or radiological signs of heart failure or LVEF less than 0.40. Aldosterone blockade in patients without significant renal dysfunction§ or hyperkalemia‖ who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either diabetes or heart failure. (See Section 7.12.6.)
Beta-Blockers	Start in all patients. Continue indefinitely. Observe usual contraindications. (See Section 7.12.7.)

STEMI = ST-elevation myocardial infarction; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; BMI = body mass index; INR = international normalized ratio; ACE = angiotensin converting enzyme; MI = myocardial infarction; CHF = congestive heart failure; LVEF = left ventricular ejection fraction.
*Non–HDL-C = total cholesterol minus HDL-C.
†Treat to a goal of non–HDL-C substantially less than 130 mg/dL.
‡Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.
§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.
‖Potassium should be less than 5.0 mEq/L.Modified with permission from Smith et al. Circulation 2001;104:1577-9 (68).

Modified from Smith et al. Circulation 2001;104:1577-9 (68).

severely limit their ability to exercise, or other absolute contraindications to exercise testing (1075). *(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)***

Exercise testing after STEMI may be performed to 1) assess functional capacity and the patient's ability to perform tasks at home and at work; 2) establish exercise parameters for cardiac rehabilitation; 3) evaluate the efficacy of the patient's current medical regimen; 4) risk-stratify the post-patient with STEMI according to the likelihood of a subsequent cardiac event (1076-1080); 5) evaluate chest pain symptoms after STEMI; and 6) provide reassurance to patients regarding their functional capacity after STEMI as a guide to return to work.

Patients who receive reperfusion therapy have a smaller infarct size (1081). Coronary angiography is frequently performed during hospitalization due to recurrent chest pain, which identifies many patients with severe disease who subsequently undergo revascularization (1082). The low cardiac event rate after discharge in patients with STEMI who are successfully reperfused substantially reduces the predictive accuracy of early exercise testing. The ability to perform an exercise test 1 month after STEMI provides a favorable prognosis irrespective of the test results (1075).

Low-level exercise testing appears to be safe if patients have undergone in-hospital cardiac rehabilitation, including low-level exercise, have had no symptoms of angina or heart failure, and have a stable baseline ECG 48 to 72 hours before the exercise test. Two different protocols have been used to determine the end points of these very early exercise tests (1083-1085):

The traditional submaximal exercise test (done at 3 to 5 days in patients without complications) incorporates a series of end points, including a peak heart rate of 120 to 130 bpm or 70% of maximal predicted heart rate for age, a peak work level of 5 metabolic equivalents (METs), or clinical or ECG

end points of mild angina or dyspnea, ST-segment depression greater than 2 mm, exertional hypotension, or 3 or more consecutive premature ventricular contractions, whichever end point is reached first. The second protocol is performance of a symptom-limited exercise test (done at 5 days or later) without stopping for target heart rates or MET levels. Although this level will result in a higher frequency of abnormal exercise tests, the prognostic value of ST depression that occurs at higher work levels in deconditioned patients is uncertain. The safety of early symptom-limited exercise testing is based on relatively limited data; therefore, clinical judgment must be used (1075). The results of this symptom-limited test can also be used to establish intensity and target heart rate during cardiac rehabilitation.

The duration of exercise is also known to be an important predictor of outcomes, and the ability to perform at least 5 METs without early exercise ST depression and show a normal rise in systolic blood pressure is important in constituting a negative predictive value (1086,1087). The optimum time for performing the exercise test after STEMI remains unresolved. It is argued that a predischarge exercise test provides psychological benefits to the patient and will permit detection of profound ischemia that could be associated with postdischarge cardiac events that might occur before a scheduled 3- to 6-week postdischarge, symptom-limited stress test. It also provides parameters for cardiac rehabilitation exercise programs. On the other hand, deferring exercise testing until approximately 3 weeks after STEMI in clinically low-risk patients appears safe and reasonable and enables more optimal assessment of functional capacity. It is the consensus of this Writing Committee that patients without complications who have not undergone coronary arteriography before discharge from the hospital and who might be potential candidates for revascularization procedures should undergo exercise electrocardiography before or just after discharge.

7.11.1.2. Role of Echocardiography

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the role of echocardiography. (See Sections 7.11.1.3, 7.11.1.4, and 7.11.1.5 for additional discussion on imaging considerations.)

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 the ACC/AHA/ASE 2003 Guideline Update for Clinical Application of Echocardiography (226).) *(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 postdischarge 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 4 or more days after STEMI to assess myocardial viability when 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 re-evaluation 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)*

The widespread availability, portability, and relatively low cost of echocardiography have resulted in its increased use as a practical and reliable means of assessing both global ventricular function and regional wall-motion abnormalities. Transthoracic imaging and Doppler techniques are generally sufficient for evaluating patients with suspected or documented ischemic heart disease. However, transesophageal echocardiography may be needed in some patients, particularly those with serious hemodynamic compromise but nondiagnostic transthoracic echocardiography studies. The uses of echocardiography in STEMI are discussed in detail in the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography (226).

Assessment of Prognosis and Complication. Echocardiography assesses global and regional ventricular function. The sum of segmental wall-motion abnormalities may overestimate infarct size because it includes regions of prior infarction and areas with ischemic stunning or hibernation of myocardium. However, LVEF and echocardiographically derived infarct size are predictive of early and late complications and mortality (1088-1091).

Echocardiography can be used to evaluate at the bedside, when needed, virtually any complication of STEMI. These complications include acute MR, cardiogenic shock, infarct

expansion, VSR, intracardiac thrombus, and pericardial effusion.

Assessment of Therapy. Given the frequent use of reperfusion therapy (fibrinolytic agents or primary angioplasty) in patients with STEMI, assessment of myocardial salvage is an important clinical issue. After successful reperfusion, myocardial stunning may occur and may last for days to months. Wall-motion segments that demonstrate hypokinesia or akinesia at rest but improved function during low-dose dobutamine infusion often recover contractility (1092-1101), which suggests that these segments are stunned. Failure of such segments to show improvement suggests functional recovery is unlikely to occur (1092-1101). These issues are discussed in more detail in the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography (226).

Predischarge Evaluation With Stress Echocardiography. The role of exercise testing in evaluation of patients with STEMI before discharge is discussed in Section 7.11.1.1. As previously noted, the ability to perform an exercise test 1 month after STEMI provides a favorable prognosis regardless of test results (1075). The incremental value of exercise echocardiography over regular exercising testing after STEMI has not been established. Prospective natural history studies are difficult to accomplish because many clinicians now perform angiography and recommend revascularization in patients with significant coronary obstructions. Echocardiography or perfusion imaging (see Section 7.11.1.3) should be added to exercise testing whenever baseline abnormalities are expected to compromise ECG interpretation.

Although serious complications have been reported (1093), general experience suggests that pharmacological stress echocardiography with a graded protocol and with low doses of dobutamine initially appears to be feasible and safe when performed 4 to 10 days after STEMI (1092,1094-1102). Pharmacological challenge can substitute for exercise in predischarge functional testing for ischemia in patients with limited exercise capacity and can help in assessing myocardial viability early after STEMI (1092,1094,1103-1112). Beta-blockade may limit the sensitivity of dobutamine echocardiography in assessing ischemia.

7.11.1.3. Exercise Myocardial Perfusion Imaging

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the role of exercise myocardial perfusion imaging. (See Sections 7.11.1.2, 7.11.1.4, and 7.11.1.5 for additional discussion on imaging considerations.)

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)*

Before the use of reperfusion therapy, the prognostic value of exercise myocardial perfusion imaging was found to be superior to that of exercise ECG testing (1113-1116). Pharmacological stress perfusion imaging was shown to have predictive value for postinfarction cardiac events (1117-1119). The key issues are whether these results apply to current patient populations in the reperfusion era and whether myocardial perfusion imaging is worth the additional cost for risk stratification (1120). The same issues outlined previously with respect to exercise echocardiographic testing apply to this methodology. In patients with STEMI who have received fibrinolytic therapy, several studies using myocardial perfusion imaging have found that it is less valuable than previously thought for risk stratification (1121-1123), primarily because of the low rate of late cardiac events.

In patients in the current era who have not received reperfusion therapy, particularly those who have not undergone revascularization, the same considerations regarding subsequent patient outcome that were outlined above for exercise ECG testing apply. There is evidence that myocardial perfusion imaging is useful for risk stratification in such patients, despite their better overall prognosis (1124). It appears likely that the previously demonstrated superiority of stress myocardial perfusion imaging probably continues to apply to this population, although there is limited evidence on this point. Prospective studies are difficult to conduct because clinicians frequently intervene in patients with abnormal predischarge stress perfusion imaging studies.

Myocardial perfusion imaging with either Tl 201 (1125), Tc 99m sestamibi (1126), or Tc 99m tetrofosmin can assess infarct size. The measurement of infarct size by any one of these techniques is significantly associated with subsequent patient mortality after fibrinolytic therapy (1125-1127). Data are also emerging to suggest that vasodilator stress nuclear scintigraphy is safe and can be used for early (48 to 72 hours) risk stratification (1128). The ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging, a revision of the 1995 guidelines, stress the ability of pharmacological stress perfusion imaging to risk-stratify patients after STEMI early and safely, thereby facilitating the development of clinical strategies (239).

Recommended strategies for exercise test evaluations after STEMI are presented in Figure 36. These strategies and the data on which they are based are reviewed in more detail in the ACC/AHA 2002 Guideline Update for Exercise Testing (1075).

7.11.1.4. Left Ventricular Function

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the importance of measurement of LV function. Either of the above imaging techniques can provide clinically useful information.

Class I

Left ventricular ejection fraction should be measured in all STEMI patients. *(Level of Evidence: B)*

Assessment of LV function after STEMI has been shown to be one of the most accurate predictors of future cardiac events in both the prereperfusion (1129) and the reperfusion (1130,1131) eras. Multiple techniques for assessing LV function of patients after STEMI have important prognostic value. Because of the dynamic nature of LV function recovery after STEMI, clinicians should consider the timing of the imaging study relative to the index event when assessing LV function. (See Table 6 of the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography for further discussion of the impact of timing on assessment of LV function and inducible ischemia) (226). The assessment can include such basic factors as clinical estimates based on patients' symptoms (e.g., exertional dyspnea, functional status), physical findings (e.g., rales, murmurs, elevated jugular venous pressure, cardiomegaly, S_3 gallop), and measurement of ejection fraction by contrast ventriculography, radionuclide ventriculography, and 2-dimensional echocardiography. Zaret and colleagues (1130) found that an LVEF less than 0.30 as assessed by radionuclide ventriculography was still predictive of mortality in patients surviving infarction treated with fibrinolytic therapy, despite the significantly reduced mortality of these patients compared with those in the prereperfusion era. White and colleagues (1132) performed contrast left ventriculography in 605 patients 1 to 2 months after MI. They found that postinfarction LV dilation, demonstrated by increased end-systolic volume greater than 130 ml, was an even better predictor of mortality after MI than an LVEF less than 0.40 or increased end-diastolic volume. In patients with normal ejection fractions, however, end-systolic volume did not provide any further stratification according to risk.

Assessment of LV function by different techniques may produce different results. The SOLVD (Studies Of Left Ventricular Dysfunction) investigators compared LVEF determined by echocardiography or radionuclide angiography and noted higher mortality for patients with LVEF less than 0.35 by echocardiography than for patients with the same value determined by the radionuclide technique (1133). LVEFs derived by radionuclide angiography and by cardiac catheterization were compared in the SAVE study, with higher values derived by catheterization (924). Radionuclear and catheterization-derived LVEF were poorly correlated, but lower values by either technique predicted a worse prognosis. In some circumstances, assessment of ventricular function by several techniques may be useful.

7.11.1.5. Myocardial Viability

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses techniques for assessing myocardial viability. Either of the above imaging techniques can provide clinically useful information.

As previously noted, LV function is a well established and powerful predictor of outcome after STEMI. In some patients, LV dysfunction results from necrosis and scar formation. In others, viable but dysfunctional myocardium contributes to LV dysfunction and may be significantly reversible with revascularization. Myocardial hibernation (chronic low-flow state associated with depressed myocardial function) (1134) and stunning (depression of ventricular function after acute ischemia despite adequate restoration of blood flow) (1135) contribute to the potential reversibility of ventricular function. Up to one third of patients with significant ischemic LV dysfunction may improve with revascularization (1136). Therefore, the distinction between ventricular dysfunction caused by fibrosis and that arising from viable but dysfunctional myocardium may have important prognostic and therapeutic implications.

Several noninvasive imaging modalities have been established as predictors of myocardial viability. Radionuclide imaging and dobutamine echocardiography have acceptable accuracy in predicting recovery of regional wall-motion abnormalities (239). More recently, relatively small studies have suggested the ability of viability studies to identify patients most likely to benefit from revascularization in terms of symptoms and natural history (1137-1140). These data are reviewed in more detail in the ACC/AHA/ASNC Guidelines for Cardiac Radionuclide Imaging (239) and the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography (226). Positron emission tomography, although not currently as widely available as other radionuclide techniques, may provide slightly better overall accuracy in predicting recovery of regional function (1141). More recently, contrast-enhanced magnetic resonance imaging has demonstrated promising results in predicting improvement of regional myocardial function in patients after STEMI (1142-1144).

The data noted above suggest that assessment of myocardial viability after STEMI, particularly in patients with severe LV dysfunction, may identify those with the highest risk, in whom revascularization can be of clinical benefit. However, myocardial viability remains incompletely understood. Viability testing is not a standard until more conclusive diagnostic efficacy studies are performed to demonstrate patient benefit.

7.11.1.6. Invasive Evaluation

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 2002 Guideline Update for the Management of Patients With Chronic Stable Angina) (71). *(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

Catheterization and revascularization may be considered as part of a strategy of routine coronary arteriography for risk assessment after fibrinolytic therapy (see Section 6.3.1.6.4.7). *(Level of Evidence: B)*

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)*

In contrast to noninvasive testing, coronary arteriography provides detailed structural information to allow an assessment of prognosis and to provide direction for appropriate management. Indications for coronary arteriography are interwoven with indications for possible therapeutic plans such as PCI or CABG. All survivors of STEMI who are candidates for revascularization therapy with spontaneous ischemia, intermediate- or high-risk findings on noninvasive testing, hemodynamic or electrical instability, mechanical defects, prior revascularization, or high-risk clinical features should be considered for coronary arteriography. Percutaneous coronary intervention or CABG may be considered in these patients if they are found to have significant obstructive coronary artery disease (1145-1147).

Given the adverse clinical consequences of recurrent infarction, it would be highly desirable to minimize the chance of its occurrence after initial treatment for STEMI. Routine referral for angiography of all patients after fibrinolytic therapy is intuitively attractive and supported indirectly by retrospective analyses from trials of fibrinolytic therapy that suggest that patients treated with PCI during the index hospitalization had a lower risk of recurrent MI and a lower 2-year mortality (512). However, previous randomized trials testing a strategy of routine catheterization after fibrinolysis suggested that such an approach was deleterious (480,503,505,516,1148). However, the previous trials were conducted in an era during which aspirin was inconsistently administered, high doses of UFH without monitoring of activated clotting time were used, and the interventional catheters, radiographic imaging equipment, and supportive antiplatelet agents were suboptimal. The Writing Committee encourages contemporary research into the benefit of routine catheterization versus watchful waiting after fibrinolytic therapy in the contemporary era (1149,1149a). See Section 6.3.1.6.4.7.

7.11.1.7. Ambulatory ECG Monitoring for Ischemia

The value of ambulatory ECG monitoring in assessing reversible myocardial ischemia and the risk of a subsequent coronary event early after MI has been evaluated in a number of studies (1150-1157). Up to 25% of patients will show residual ischemia detected on ambulatory ECG monitoring. Most episodes of transient myocardial ischemia are silent and occur at rest or during times of low-level physical activity or mental stress (1158). During long-term follow-up studies, a number of investigators have reported that the presence of ischemia detected by ambulatory ECG monitoring in the postinfarction period is predictive of a subsequent poor outcome and increases the risk of cardiac events (1150-1157). One study found that the odds ratio for patients with ambulatory ischemia, compared with those without it, was 2.3 for death or nonfatal MI at 1 year (1157).

Despite the promising initial results with ambulatory ECG monitoring, the totality of evidence does not support a general statement about its role in patients with STEMI. Some studies have shown that the results of ambulatory ECG monitoring could be predicted from exercise test data (1152,1155), whereas others have found that additional prognostic information could be obtained by ambulatory ECG monitoring in postinfarction patients (1153). At present, a cost-effective strategy has not been developed to identify patients who are at increased risk for ambulatory ischemia and in whom ambulatory ECG monitoring might be more helpful for stratification into high- and low-risk subgroups for future coronary events.

7.11.1.8. 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,

heart rate variability, micro T-wave alternans, and T-wave variability) in patients recovering from STEMI. ***(Level of Evidence: B)***

A number of noninvasive strategies have been used to try to identify patients at high risk for arrhythmic events. Although most of these measure some aspect of the excessive activation of the autonomic nervous system commonly observed in high-risk patients with LV dysfunction, others measure impulse conduction through the infarct zone. Thus, noninvasive determinants of arrhythmia risk encompass measurement of changes in ventricular repolarization, alterations of autonomic tone, and delayed and disordered myocardial conduction.

The most frequently used techniques are signal-averaged or high-resolution ECG, heart rate variability, baroreflex sensitivity, and T-wave alternans. Signal-averaged electrocardiography identifies delayed, fragmented conduction in the infarct zone in the form of late potentials at the terminus of the QRS complex and represents an anatomic substrate that predisposes the patient to re-entrant VT. Kuchar et al. (1159) reported that late potentials predict an increased incidence of sudden death in the post-MI patient population. Gomes et al (1160) found late potentials to be the best single predictor when considering Holter monitoring and ejection fraction and found that they contributed independently to a combined index, although the positive predictive value of each was poor. The filtered QRS duration was the most predictive feature of signal-averaged electrocardiography in a Cardiac Arrhythmia Suppression Trial (CAST) substudy (1161). More recent studies have shown that reperfusion therapy reduces the incidence of late potentials after STEMI (1162). In the setting of frequent use of fibrinolysis, the predictive value of signal-averaged electrocardiography has been variable (1163-1165).

Heart rate variability, an analysis of the beat-to-beat variation in cycle length, largely reflects the sympathovagal interaction that regulates heart rate. Heart rate variability can be quantified in a number of ways, with either time- or frequency-domain parameters (1166). Low heart rate variability, indicative of decreased vagal tone, is a predictor of increased mortality, including sudden death, in patients after MI (1166,1167) and may add significant prognostic information to other parameters (1167). The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study (1168) was a prospective multicenter study that enrolled 1284 patients with a recent (fewer than 28 days) MI. Decreased heart rate variability was a significant and independent predictor of cardiac mortality (hazard ratio 3.2, p equals 0.005) (1168).

The predictive value of heart rate variability after STEMI, although significant, is modest when used alone. In combination with other techniques, its positive predictive accuracy improves. The most practical, feasible, and cost-efficient combination of noninvasive predictive tests with heart rate variability remains to be determined.

Baroreceptor sensitivity also quantifies the influence of parasympathetic tone on the heart. It is measured as the slope of a regression line relating beat-to-beat heart rate change in response to a change in blood pressure, often accomplished by giving a small bolus of phenylephrine (1169). Reductions in baroreflex sensitivity have been associated with an increased susceptibility to arrhythmic events and sudden death in experimental models and initial clinical reports (1170-1172).

Finally, abnormalities in ventricular repolarization are detectable by microvolt alterations of T-wave amplitude, or T-wave alternans. In experimental preparations, the presence of T-wave alternans was predictive of a lower fibrillation threshold. Clinical studies have demonstrated that T-wave alternans is associated with ventricular arrhythmias during EP testing, as well as with clinically evident arrhythmias. Microvolt T-wave alternans was subsequently shown to be associated with inducible ventricular arrhythmias during programmed ventricular stimulation and spontaneous arrhythmic events (1173,1174).

The clinical applicability of these tests to the post-STEMI patient is in a state of evolution. Although the negative predictive value of most of these tests taken in isolation is high (generally greater than 90%), the positive predictive value is unacceptably low (less than 30%). Whereas the positive predictive value of noninvasive testing for future arrhythmic events can be modestly increased by combining several test results, the therapeutic implications of positive findings are unclear. Insufficient data are available to indicate whether general therapies, such as beta-adrenoceptor blockade, ACE inhibition, and revascularization procedures, or specific interventions, such as treatment with amiodarone or an ICD, targeted toward high-risk patients identified by a combination of noninvasive tests after MI can more favorably impact mortality (1175). The widening indications for ICD implantation in patients with LV dysfunction may encourage the use of these studies to find the lowest-risk patients (i.e., those without any high-risk markers whatsoever) to avoid ICD implantation. Finally, it is difficult to justify the costs of the routine use of these procedures in the absence of demonstrated clinical benefits. Until these issues are resolved, these tests are used only to support routine management and risk assessment.

7.12. Secondary Prevention

Class I

Patients who survive the acute phase of STEMI should have plans initiated for secondary prevention therapies. ***(Level of Evidence: A)***

Secondary prevention therapies, unless contraindicated, are an essential part of the management of all patients with STEMI (Table 32) (68), regardless of sex (69,1176). Inasmuch as atherosclerotic vascular disease is frequently found in multiple vascular beds, the physician should search

for symptoms or signs of peripheral vascular disease or cerebrovascular disease in patients presenting with STEMI.

Approximately 70% of CHD deaths and 50% of MIs occur in patients who have previously established coronary artery disease (677). It is estimated that the likelihood of fatal and nonfatal MI is 4 to 7 times higher in patients with apparent coronary disease. The institution of secondary prevention therapies and risk reduction strategies in patients recovering from STEMI represents major opportunities to reduce the toll of cardiovascular disease.

Smoking cessation, aggressive lipid lowering, control of hypertension and diabetes, and prophylactic use of aspirin, beta-blockers, and ACE inhibitors are key components of secondary prevention that have a demonstrated benefit. Dietary cholesterol contributes to elevations in LDL-C and should be included in the list of dietary modifications (reduction in total calories, saturated fat, cholesterol, and salt and increase in vegetables, fruits, and grain fiber) given to the post-STEMI patient. These changes are both directly beneficial and aid in hypertension control and lipid lowering. The specifics of these therapies and recommendations for their use are discussed in the following sections (68).

Secondary prevention services remain discouragingly underutilized (1177) despite the compelling evidence for and large magnitude of their benefits (1178-1180). The ACC and AHA urge all healthcare providers to implement systems that ensure the reliable identification of patients who can benefit from secondary prevention interventions and to ensure that these interventions occur (1181,69). Evidence exists that lifestyle modifications (as discussed below), including regular physical exercise, weight reduction, cessation of cigarette smoking, and stress reduction strategies, have a favorable impact on blood coagulation, fibrinolysis, and platelet reactivity, shifting the patient to a less atherogenic and prothrombotic state (Table 32) (68,1182). Referral to outpatient cardiac rehabilitation can aid in attainment of these goals (1183,1184).

Many institutions have clinical pathways for improving quality of care of patients with STEMI (205). Use of clinical pathways or other management protocols in hospital settings has resulted in improved adherence to therapy by CHD patients and better cholesterol control. The Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) focused on the initiation of therapy with aspirin, beta-blockers, ACE inhibitors, statins, diet, and exercise in persons with established CHD before hospital discharge (1185). There was a significant increase in the use of aspirin, beta-blockers, ACE inhibitors, and statin therapy. The program used postdischarge follow-up visits to titrate the statin dose to achieve an LDL-C level less than 100 mg/dL. One year after discharge, 91% of patients were being treated with cholesterol-lowering therapy, and 58% were at treatment goals. These results suggest that the initiation of treatment during hospitalization for CHD adds needed emphasis to the importance of cholesterol-lowering treatment along with other cardiac medications. There was also a reduction in recurrent MI and 1-year mortality. Evidence exists that adherence to practice guidelines for the management of patients after STEMI is associated with significant reductions in short- and long-term mortality (1186).

7.12.1. 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 1 nitroglycerin dose sublingually) 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)***

Once STEMI has occurred, secondary prevention, including aggressive risk factor management through medical and lifestyle therapy, is the mainstay of therapy.

It is important for providers in the inpatient setting to communicate with the patient's primary care provider to facilitate coordination of care. The discharge summary should include the patient's medical, psychological, and functional status; prescribed medication and lifestyle regimens; and the patient's living/social support situation (1187).

Effective education is critical to enlist patients' full participation in therapeutic regimens and secondary prevention efforts and to minimize their natural concerns and anxieties. It ideally leads to a patient who is better informed and more satisfied with his or her care and who is also able to achieve a better quality of life and improved survival (71,688,1188-1190). In general, the outcomes of educational interventions depend on the outcome studied (e.g., largest for knowledge change, smallest for behavioral and psychological outcomes) (692) and the strategies applied (688).

Principles of Patient Education. A thorough discussion of the philosophies of and approaches to patient education is beyond the scope of this guideline. There are useful reviews on this topic (688,692,1191), including a few that focus on ischemic heart disease (1192-1194). Well-designed educational programs can improve patients' knowledge and in some instances can improve outcomes (688,1195). These approaches form the basis for commonly used educational programs, such as those conducted before CABG (1196) and after MI (690,1197). A variety of guidelines should be fol-

lowed to help ensure that educational efforts are successful (71):

1. Assess the patient's baseline understanding. This not only establishes a starting point for education but also engages the patient. Healthcare providers are often surprised at the idiosyncratic notions that patients have about their own medical conditions and therapeutic approaches (688,1198,1199).
2. Elicit the patient's desire for information. Adults prefer to set their own agendas, and they learn better when they can control the flow of information.
3. Use epidemiological and clinical evidence. As clinical decision making becomes increasingly based on scientific evidence, it is reasonable to share that evidence with patients. Epidemiological data can assist in formulating an approach to patient education, such as conveying information on the major cardiovascular disease risk factors. Scientific evidence about the reduction in cardiovascular disease risk to be derived from risk factor modification/lowering can help persuade patients about the effectiveness of various interventions.
4. Use allied professional personnel. Even though physicians may feel constrained with the limited amount of time available for a patient encounter, interpersonal contact with and encouragement from physicians is nevertheless a vital component of the patient's overall health education. Medical encounters represent powerful "teaching moments" for initiating discussion and shaping perceptions and expectations, and they are perceived as highly credible sources of information (1200,1201). In many settings, trained health educators, many of whom specialize in diabetes or cardiac disease, are available. Personnel from disciplines such as nursing, physical therapy, nutrition, pharmacy, and others can provide reinforcement, more in-depth information, and ongoing educational support and thus have much to offer patients with ischemic heart disease (1202). Reimbursement for educational activities by these allied providers is poor, although this can also be accomplished as part of a cardiac rehabilitation program for which funding is generally available.
5. Use professionally prepared resources when available. Studies have shown that combined teaching strategies, including written and audiovisual materials in addition to verbal instruction, group approaches, and enhanced education methods, are the most effective in achieving desired outcomes (688,692,1192). The decreasing length of hospital stays has raised concern about adequate opportunity for appropriate patient education (369,697), although short educational sequences can produce outcomes comparable to lengthy sessions (690). Innovative presentation styles (e.g., programmed instruction, audiovisual techniques, and health education television programs) can produce benefits comparable to individual educational sessions (1203). Use of a single repository for all educational materials (e.g., a binder that travels with the patient) may provide consistency, document material taught, identify goals that remain, and promote independent study, an effective education strategy (688,1191).
6. Although any planned teaching strategy is better than none (688), computer-assisted instruction is the newest approach to patient education. Patients without computer access can be directed to a work station in the physician's office, clinic, hospital education department/library, or local library, where relevant pages can be printed. A review of the literature on computer-based approaches to patient education supports the use of computer-based education as an effective strategy for transfer of knowledge and skill development for patients (1204). The World Wide Web is convenient for medical personnel and patients with access to personal computers. The AHA maintains a Web site (http://www.americanheart.org) that presents detailed and practical dietary recommendations and information about heart disease, physical activity, heart attacks, and CPR. The NHLBI Web site (http://www.nhlbi.nih.gov) has links to the National High Blood Pressure Education Program, NCEP, and the NHAAP's "Act In Time to Heart Attack Signs," which have information for patients and professionals. Both the ACC's "Guidelines Applied in Practice" program (http://www.acc.org/gap/images/Discharge.gif) and the AHA's "Get With the Guidelines Hospital Tool Kit" (http://www.americanheart.org/downloadable/heart/1107_HospTool.pdf) provide discharge information as part of a separate patient-specific discharge form (Guidelines Applied in Practice) or incorporated into a patient pathway (Get With the Guidelines). The discharge information for patients reviews and documents the important lifestyle changes and drug therapies for the secondary prevention of cardiovascular disease that are part of their discharge instructions. An important issue currently receiving attention is the issue of health literacy. Studies with patients and the public have found average reading abilities do not exceed the eighth-grade level (688,695). The current recommendation is that materials be written at the sixth-grade level to ensure that the maximum number of people can read and understand them.
7. Develop an action plan with the patient for their long-term management. If it is necessary to convey a great deal of information to patients about their condition, be cognizant of the patient's level of sophistication, readiness to change, prior educational attainment, language barriers, relevant clinical factors, and social support. A realistic goal might be to motivate an internal change that results in the patient's desire to ask for information on an important topic such as smoking cessation (691). It may be counterproductive to attempt to coax a patient into simultaneously changing several behaviors, such as smoking, diet, and exercise, and taking (and purchasing) multiple new medications. Achieving optimal adherence often requires talking to patients to identify barriers to

compliance such as complex regimens and cost of medications (1205) and addressing these barriers through problem solving with the patient.

8. Involve family members in educational efforts. It is advisable and often essential to include family members in educational efforts. Many activities require the participation of family members; an example is meal preparation. Efforts to encourage smoking cessation, weight loss, or increased physical activity may be enhanced by enlisting the support of family members who can reinforce the behavior and may themselves benefit from participation.
9. Remind, repeat, and reinforce. Almost all learning deteriorates without reinforcement. At regular intervals, the patients' understanding should be reassessed, and key information should be repeated as warranted. Feedback is a powerful motivator, and patients should be congratulated for progress even when their ultimate goals are not fully achieved. Even though the patient who has reduced his or her use of cigarettes from 2 packs to 1 pack per day has not quit smoking, that 50% reduction in exposure is important and may simply represent a milestone on the path to complete cessation (688).

The secondary prevention targets for post-STEMI patients, around which education and follow-up/management should occur, are discussed in the following sections.

Within 6 years after a recognized heart attack, 18% of men and 35% of women will have another heart attack (46); most episodes of cardiac arrest occur within 18 months after hospital discharge for STEMI (1206). Thus, it is critical that patients and family members are educated in advance about recognition of acute ischemic symptoms and the appropriate action steps to take to ensure early evaluation and treatment (see Section 3.3). Furthermore, patients who have had a STEMI have a sudden death rate that is 4 to 6 times that of the general population (46). Thus, family members of patients with STEMI should be advised to learn CPR and should be given community resources to obtain this training. In addition, research has shown that patients whose family members received a social support intervention in conjunction with being taught CPR reported better psychosocial adjustment and less anxiety and hostility than those whose families received CPR training only or CPR training with risk factor education. Family members should be referred to a CPR program that combines CPR training with social support (132,133). (See Section 4.2.)

7.12.2. Lipid Management

Class I

1. **Dietary therapy that is low in saturated fat and cholesterol (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol) should be started on discharge after recovery from STEMI. Increased consumption of the following should be encouraged: omega-3 fatty acids, fruits, vegetables, soluble (viscous) fiber, and whole grains. Calorie intake should be balanced with energy output to achieve and maintain a healthy weight. *(Level of Evidence: A)***
2. **A lipid profile should be performed, or obtained from recent past records, for all STEMI patients, preferably after they have fasted and within 24 hours of symptom onset. *(Level of Evidence: C)***
3. **The target LDL-C level after STEMI should be substantially less than 100 mg/dL. *(Level of Evidence: A)***
   a. **Patients with LDL-C 100 mg/dL or above should be prescribed drug therapy on hospital discharge, with preference given to statins. *(Level of Evidence: A)***
   b. **Patients with LDL-C less than 100 mg/dL or unknown LDL-C levels should be prescribed statin therapy on hospital discharge. *(Level of Evidence: B)***
4. **Patients with non–high-density lipoprotein cholesterol (HDL-C) levels less than 130 mg/dL who have an HDL cholesterol level less than 40 mg/dL should receive special emphasis on nonpharmacological therapy (e.g., exercise, weight loss, and smoking cessation) to increase HDL. *(Level of Evidence: B)***

Class IIa

1. **It is reasonable to prescribe drug therapy at hospital discharge to patients with non–HDL-C greater than or equal to 130 mg/dL, with a goal of reducing non–HDL-C to substantially less than 130 mg/dL. *(Level of Evidence: B)***
2. **It is reasonable to prescribe drugs such as niacin or fibrate therapy to raise HDL-C levels in patients with LDL-C less than 100 mg/dL and non–HDL-C less than 130 mg/dL but HDL-C less than 40 mg/dL despite dietary and other nonpharmacological therapy. Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician. *(Level of Evidence: B)***
3. **It is reasonable to add drug therapy with either niacin or a fibrate to diet regardless of LDL and HDL levels when triglyceride levels are greater than 500 mg/dL. In this setting, non–HDL-C (goal substantially less than 130 mg/dL) should be the cholesterol target rather than LDL-C. Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician. *(Level of Evidence: B)***

Early secondary prevention trials conducted before the use of statin therapy, using the then-available drugs and diet to lower cholesterol, demonstrated significant reductions of 25% in nonfatal MIs and 14% in fatal MIs (59). Subsequently, a growing body of evidence derived mainly from large randomized clinical trials of statin therapy has firmly established the desirability of lowering atherogenic serum lipids in patients who have recovered from a STEMI.

The Scandinavian Simvastatin Survival Study (1207) reported results in 4444 men and women with CHD and moderate hypercholesterolemia observed over 5.4 years. Coronary heart disease mortality was reduced by 42% and total mortality by 30% among those receiving simvastatin compared with placebo. The relative risk reduction seen in this trial was similar among those with the lowest quartile compared with the highest quartile of baseline serum LDL-C. The CARE trial was a similar study in a population of patients who had recovered from an earlier MI and whose total cholesterol (mean 209 mg/dL) and LDL-C (mean 139 mg/dL) were essentially the same as the average for the general US population. In this trial, 4159 patients were randomly assigned to either 40 mg of pravastatin a day or placebo. After a median follow-up of 5 years, there was a significant reduction in the primary end point of fatal CHD and nonfatal confirmed MIs in the pravastatin cohort (3% ARD; 24% RRR; p equals 0.003) (1208).

The results of the large Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study have been reported for more than 9000 patients randomly assigned to either placebo or 40 mg of pravastatin daily (1209). The trial was conducted in patients with a prior history of MI or unstable angina. Patient age at time of entry ranged from 21 to 75 years. The LIPID trial was stopped prematurely because of the efficacy of pravastatin in reducing major cardiovascular events, including significant decreases in CHD deaths (1.9% ARD; 24% RRR), total mortality rate (3.1% ARD; 22% RRR), and stroke (0.8% ARD; 19% RRR). Benefit has also been seen in patients with symptomatic coronary disease who were treated with fluvastatin. In the Lescol in Severe Atherosclerosis (LiSA) Study, patients with symptomatic CHD and hypercholesterolemia who were given fluvastatin had 71% fewer cardiac events than those in the placebo group (1210).

The effect of cholesterol lowering combined with low-intensity oral anticoagulation on late saphenous vein graft status has also been investigated (1211). In an angiographic trial attempting to reduce atherosclerosis in saphenous vein grafts after CABG surgery, aggressive lowering of LDL to less than 100 mg/dL with lovastatin 40 to 80 mg daily (and 8 g of cholestyramine daily, if needed), in addition to a Step I AHA diet, achieved a significant reduction (2.7% ARD; 29% RRR) in obstructive changes in the vein grafts at 4 to 5 years compared with moderate lipid lowering to an LDL-C of 132 to 136 mg/dL (1211). There was no benefit of low-dose warfarin therapy at 5 years. The results of 7.5-year follow-up revealed significant reductions of 30% in revascularization and 24% for the composite end point (death, nonfatal MI, stroke, CABG, or PCI) in the group treated with aggressive lipid-lowering therapy. The investigators concluded that the study provided support for the NCEP recommendation that LDL-C levels should be reduced to less than 100 mg/dL in patients who have coronary artery disease (1212).

The Heart Protection Study (1213) trial randomized more than 20 000 men and women aged 40 to 80 years with coronary disease, other vascular disease, diabetes, and/or hypertension to simvastatin 40 mg or placebo for a mean follow-up of 5 years. The primary end point, total mortality, was significantly reduced with statin treatment (1.8% ARD; 12% RRR, p equals 0.0003). The advantages of simvastatin therapy were demonstrated in all important prespecified subgroups, including women, patients more than 75 years old, diabetics, and individuals with baseline LDL-C of less than 100 mg/dL. The study supports the benefit of statin therapy for all groups and argues for the use of statins among patients with CHD and LDL-C values 100 to 129 mg/dL who had previously been considered candidates for diet and lifestyle changes to lower LDL-C before implementation of statin therapy (59).

Approximately 25% of patients who have recovered from STEMI demonstrate desirable total cholesterol values but a low HDL-C fraction on a lipid profile. Low HDL-C is an independent risk factor for development of coronary artery disease (1214), and therefore a rationale exists for attempting to raise HDL-C when it is found to be low in the patient with coronary artery disease. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (1215) revealed that modification of other lipid risk factors can reduce risk for CHD when LDL-C is in the range of 100 to 129 mg/dL. In this trial, male patients with a relatively low LDL-C (mean 112 mg/dL) were treated with gemfibrozil for 5 years. Gemfibrozil therapy, which raised HDL-C and lowered triglycerides, reduced the primary end point of fatal and nonfatal MI (4.4% ARD; 22% RRR) without significantly lowering LDL-C levels. There was no evidence of an increased risk of non-CHD mortality. This trial supports the concept that when LDL-C is in the range of 100 to 129 mg/dL, the use of other lipid-modifying drugs (e.g., fibrates) is a therapeutic option if the patient has a low HDL-C (less than 40 mg/dL).

The effect of hypertriglyceridemia is somewhat controversial because in many cases, the triglyceride level varies inversely with HDL-C levels. However, if hypertriglyceridemia (triglyceride greater than 200 mg/dL) exists after lifestyle changes such as diet and exercise and statin therapy have been initiated, it is recommended that additional therapy be initiated to lower triglycerides for patients with established CHD (59). In this setting, the target goal of therapy should be non–HDL-C less than 130 mg/dL.

Diet and drug treatments available for the correction of lipid abnormalities are as effective in the elderly as in the young. Clinical trials have shown that such treatment can reduce total mortality up to age 70 years (1207) and the rate of recurrent coronary events up to age 75 years (1208). In addition, the PROSPER trial (1208) studied the value of lipid control for the prevention of initial coronary events in 5804 older persons (2804 men and 3000 women aged 70 to 82 years). Treatment with pravastatin 40 mg daily resulted in a reduction in LDL-C by 34% and significantly reduced the primary end point (CHD death, nonfatal MI, and fatal or nonfatal stroke) over 3.2 years (2.1% ARD; 15% RRR). Unlike previous trials involving elderly patients, the risk of stroke in PROSPER was unaffected, possibly because of the relatively

short duration of the trial. Among elderly patients, other risk factors such as high blood pressure, cigarette smoking, and diabetes are frequently present. Thus, it is especially important in this group, as in younger patients, to develop comprehensive treatment programs, such as cardiac rehabilitation, to address all risk factors that might contribute to future CHD events in addition to treating their dyslipidemia.

The early secondary prevention trials of statins specifically excluded patients with STEMI in the acute phase. Thus, although the data supporting the efficacy and benefit of statin therapy for patients after STEMI are robust, statin therapy in the early studies was started 4 to 6 months after STEMI. Subsequent studies have addressed the potential benefits of early initiation of statin therapy during hospitalization for acute coronary syndrome. The results from several of these studies, wherein statins were initiated during the hospital phase of acute coronary syndromes, indicate improved cardiovascular outcomes. The Lipid-Coronary Artery Disease trial (1216) randomized 126 patients with acute coronary syndrome to early treatment with pravastatin with or without cholestyramine or niacin therapy versus usual care. Treatment initiated during hospitalization significantly reduced clinical events at 2 years. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial randomized 3086 patients admitted for acute coronary syndrome to treatment with atorvastatin 80 mg per day or placebo within 96 hours after admission (1217). The primary end point of death, nonfatal MI, resuscitated cardiac arrest, or recurrent severe myocardial ischemia was reduced from 17.4% to 14.8% (p equals 0.048) by treatment with atorvastatin. The major clinical benefits were fewer strokes and a lower risk of severe recurrent ischemia among those treated with atorvastatin. In the Swedish Registry of Cardiac Intensive Care of nearly 20 000 patients, a 25% reduction in mortality at 1 year was observed among patients when statin therapy was initiated before hospital discharge (1218). Early initiation of therapy has been recommended by the NCEP (59). The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 study (PROVE-IT-TIMI 22) (1219) compared intensive lipid-lowering therapy to moderate lipid-lowering therapy initiated within 10 days after hospital admission in 4162 patients with acute coronary syndrome. Lipid lowering to a goal of LDL-C less than 100 mg/dL (median 95 mg/dL) with pravastatin 40 mg per day was compared with lipid-lowering to a goal of LDL-C less than 70 mg/dL (median 62 mg/dL) with atorvastatin 80 mg daily. After 2 years of therapy, the primary end point (death due to any cause, MI, unstable angina requiring rehospitalization, coronary revascularization, and stroke) was 26.3% for the group undergoing moderate lipid-lowering therapy and 22.4% in the intensive lipid-lowering group, reflecting a 16% reduction in the hazard ratio favoring intensive lipid-lowering therapy (p equals 0.005). Benefits were observed within 30 days of initiation of therapy and occurred at all levels of LDL-C, even among those patients with LDL-C less than 100 mg/dL, although the greatest benefit was seen among patients with LDL-C of 125 mg/dL or greater. The benefits were observed in all important subgroups, including men and women, young and old, and patients with and without diabetes. These data support the early, intensive treatment of patients with acute coronary syndromes to LDL-C goals substantially less than 100 mg/dL with statin therapy. Patients hospitalized with CHD who start lipid-lowering therapy before discharge have been shown to be nearly 3 times as likely to be taking medication at 6 months as those starting therapy after discharge (1220).

7.12.3. Weight Management

Class I

1. **Measurement of waist circumference and calculation of body mass index are recommended. Desirable body mass index range is 18.5 to 24.9 kg/m^2. A waist circumference greater than 40 inches in men and 35 inches in women would result in evaluation for metabolic syndrome and implementation of weight-reduction strategies. *(Level of Evidence: B)***
2. **Patients should be advised about appropriate strategies for weight management and physical activity (usually accomplished in conjunction with cardiac rehabilitation). *(Level of Evidence: B)***
3. **A plan should be established to monitor the response of body mass index and waist circumference to therapy (usually accomplished in conjunction with cardiac rehabilitation). *(Level of Evidence: B)***

Obesity is a recognized major risk factor for cardiovascular disease and an important component of the metabolic syndrome (59). The clinical criteria for the metabolic syndrome include any 3 of the following: waist circumference greater than 40 inches in men and greater than 35 inches in women; triglycerides of at least 150 mg/dL; HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure greater than 130 mm Hg systolic and greater than 85 mm Hg diastolic; and fasting blood glucose of at least 110 mg/dL. The metabolic syndrome contributes significantly to CHD risk. Its treatment has weight control and physical activity as primary strategies. Because approximately 65% of the US adult population is overweight or obese (1221), it is suggested that this risk factor be carefully addressed as part of the secondary prevention strategy for all patients after STEMI. The suggested goal should be the achievement or maintenance of a healthy weight, defined in the "Dietary Guidelines for Americans" (1222) as a body mass index from 18.5 to 24.9 kg/m^2. It is suggested that overweight patients be instructed in a weight loss regimen as part of their cardiac rehabilitation program after STEMI, with emphasis on the importance of regular exercise and a lifelong prudent diet to maintain healthy weight. Weight reduction enhances lowering of other risk factors for cardiovascular disease, including LDL-C, triglycerides, impaired glucose, and blood pressure. An initial weight loss of 10% of body weight achieved over 6 months is a recommended target. The rate of weight loss should be 1 to 2 pounds each week.

7.12.4. Smoking Cessation

Class I

1. **Patients recovering from STEMI who have a history of cigarette smoking should be strongly encouraged to stop smoking and to avoid secondhand smoke. Counseling should be provided to the patient and family, along with pharmacological therapy (including nicotine replacement and bupropion) and formal smoking cessation programs as appropriate. *(Level of Evidence: B)***
2. **All STEMI patients should be assessed for a history of cigarette smoking. *(Level of Evidence: A)***

Smoking cessation is essential for patients with STEMI. Smoking triggers coronary spasm, reduces the anti-ischemic effects of beta-adrenoceptor blockers, and doubles mortality after STEMI (1223-1225). Smoking cessation reduces rates of reinfarction and death within 1 year of quitting, but one third to one half of patients with STEMI relapse within 6 to 12 months (1226). Because exposure to secondary cigarette smoke has been identified as a risk factor, family members who live in the same household should also be encouraged to quit smoking to help reinforce the patient's effort and to decrease the risk of secondhand smoke (1227).

The most effective strategies for encouraging quitting are those that identify the patient's level or stage of readiness and provide information, support, and, if necessary, pharmacotherapy targeted at the individual's readiness and specific needs (66,1228). Houston-Miller and Taylor (1229) advocate a stepped approach to smoking cessation:

a. Provide a firm, unequivocal message to quit smoking
b. Determine whether the patient is willing to quit
c. Determine the best quitting method
d. Plan for problems associated with withdrawal
e. Set a quit date
f. Help the patient cope with urges to smoke
g. Provide additional help as needed
h. Follow-up by telephone call or visit

The stepwise strategies are summarized in Table 30 of the ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina (71).

The most effective pharmacological adjuncts for treating nicotine dependence are nicotine replacement therapy and bupropion in the sustained-release form. When these are combined with behavioral counseling, the best treatment outcomes have been reported (1230). Nicotine replacement therapy (gum and patches) has been shown to increase smoking cessation rates, particularly when combined with counseling (1231). Nicotine replacement therapy can mitigate symptoms of nicotine withdrawal in recovering patients (1232). A population-based case-control study did not find an association between nicotine patches and first-time MI (1233). Several studies have suggested that nicotine replacement therapy does not increase the risk for cardiovascular events, even in people with underlying CHD (1234-1237), although the studies had few or no patients with MI (1235-1237) and were not designed (1235) or sufficiently powered (1234) to examine cardiovascular effects. Thus, routine use of these agents is not recommended during hospitalization for STEMI because of the sympathomimetic effects of the active ingredient, nicotine. However, the dose of nicotine in gums and patches is significantly lower than that found in cigarettes and may be preferable to cigarette smoking if the patient is experiencing acute withdrawal. Therefore, at the time of discharge, if blood pressure and heart rate are stable, these agents may be used in selected patients. Clonidine has been shown to be effective in women but not men (1238); the reason for this finding is unclear. Lobeline has not been shown to have an advantage over placebo (1239-1241) but is again under investigation.

Bupropion has been shown to help smokers quit (1242,1243). Nicotine intake is reinforced by activating the central nervous system to release norepinephrine, dopamine, and other neurotransmitters. Bupropion is a weak inhibitor of the neuronal uptake of neurotransmitters. A study of 615 subjects randomly assigned to take placebo or bupropion achieved good initial quit rates with treatment augmented by brief counseling at baseline, weekly counseling during treatment, and intermittent counseling for up to 1 year (1244). Seven weeks of treatment with bupropion was associated with a smoking cessation rate of 28.8% (100 mg/d), 38.6% (150 mg/d), and 44.2% (300 mg/d); 19.6% of subjects assigned to placebo quit (p less than 0.001). At 1 year, 12.4% of the placebo group and 19.6% (100 mg/d), 22.9% (150 mg/d), and 23.1% (300 mg/d) of the bupropion group remained abstinent. The drug was well tolerated (37 [8%] of 462 stopped treatment prematurely because of headache, insomnia, or dry mouth), although the study was insufficiently powered to detect an incidence of seizures known to occur with related medications. It reduced the weight gain common in smokers who quit. Bupropion appears to be a valuable option for patients who need to quit smoking after STEMI. In an actual large group-practice setting, the combination of slow-release bupropion and minimal or moderate counseling was associated with 1-year quit rates of 24% and 33%, respectively (1243).

7.12.5. Antiplatelet Therapy

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 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)***

Class III

Ibuprofen should not be used because it blocks the antiplatelet effects of aspirin. ***(Level of Evidence: C)***

On the basis of 12 randomized trials in 18 788 patients with prior infarction, the Antiplatelet Trialists' Collaboration reported a 25% reduction in the risk of recurrent infarction, stroke, or vascular death in patients receiving prolonged antiplatelet therapy (36 fewer events for every 1000 patients treated) (263). No antiplatelet therapy has proved superior to aspirin in this population, and daily doses of aspirin between 80 and 325 mg appear to be effective (1245). The CAPRIE trial, which compared aspirin with clopidogrel in 19 185 patients at high risk for vascular events, demonstrated a modest but significant reduction in serious vascular events with clopidogrel compared with aspirin (0.51% ARD; 8.6% RRR; p equals 0.043) (742). These data suggest clopidogrel as the best alternative to aspirin in patients with true aspirin allergy.

These compelling data suggest that all patients recovering from STEMI should, in the absence of contraindications, continue taking aspirin for an indefinite period (1246). Clopidogrel or ticlopidine may be substituted in patients with true aspirin allergy.

The use of warfarin therapy for secondary prevention of vascular events in patients after STEMI is discussed in Section 7.12.11. Large randomized trials have demonstrated that oral anticoagulants, when given in adequate doses, reduce the rates of adverse outcomes, at the cost of a small increase in hemorrhagic events (1247-1249). In the Warfarin, Aspirin, Reinfarction Study (WARIS II), warfarin without aspirin in a dose intended to achieve an INR of 2.8 to 4.2 resulted in a significant reduction in a composite end point (death, nonfatal reinfarction, or thromboembolic stroke) compared with therapy with aspirin alone (16.7% versus 20.0%) (1247). Warfarin therapy resulted in a small but significant increase in major, nonfatal bleeding compared with therapy with aspirin alone (0.62% per year versus 0.17% per year). Chronic therapy with warfarin after STEMI presents an alternative to clopidogrel in patients with aspirin allergy.

A small increase in incidence of stroke in healthy men treated with aspirin was reported in both the American physician and the British doctors primary prevention studies (1250,1251). However, there has been no evidence of an increased incidence of stroke in studies in which aspirin was used for secondary prevention of coronary artery disease. These secondary prevention trials clearly indicate that in patients with clinical manifestations of atherosclerotic disease, aspirin reduces risk of stroke. It is likely that as a consequence of its antihemostatic effect, aspirin produces a small increase in risk of cerebral hemorrhage, which is masked by the beneficial effects of aspirin in patients with an increased risk for thromboembolic stroke but becomes manifest in healthy individuals at very low risk for this event.

Aspirin and NSAIDs are among the most commonly consumed drugs. An interaction between aspirin and ibuprofen on platelet function has been demonstrated in an in vivo model, with concomitant administration of ibuprofen (but not rofecoxib, diclofenac, or acetaminophen) antagonizing the irreversible platelet inhibition induced by aspirin (1252). A subsequent epidemiological study demonstrated increased all-cause and cardiovascular mortality in patients with cardiovascular disease taking aspirin plus ibuprofen compared with those taking aspirin alone, aspirin plus diclofenac, or aspirin plus other NSAIDs (1253). The use of NSAIDs in patients taking aspirin was also assessed in an observational subgroup analysis of the Physician's Health Study (1254). Regular (greater than 60 days per year) use of NSAIDs inhibited the clinical benefits of aspirin, although intermittent use (fewer than 59 days per year) had no effect. These findings suggest that ibuprofen may limit the cardioprotective effects of aspirin. Pending further data, clinicians should discourage patients with cardiovascular disease who are taking aspirin from using ibuprofen on a regular basis.

7.12.6. Inhibition of the Renin-Angiotensin-Aldosterone System

Class I

1. **An ACE inhibitor should be prescribed at discharge for all patients without contraindications after STEMI.** ***(Level of Evidence: A)***
2. **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)***
3. **An ARB should be prescribed at discharge to those STEMI patients who are intolerant of an ACE inhibitor and have either clinical or radiological signs of heart failure and LVEF less than 0.40. Valsartan and candesartan have established efficacy for this recommendation.** ***(Level of Evidence: B)***

Class IIa

In STEMI patients who tolerate ACE inhibitors, an ARB can be useful as an alternative to ACE inhibitors in the long-term management of STEMI patients, provided there are 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: B)***

Class IIb

The combination of an ACE inhibitor and an ARB may be considered in the long-term management of STEMI patients with persistent symptomatic heart failure and LVEF less than 0.40. ***(Level of Evidence: B)***

The use of ACE inhibitors early in the acute phase of STEMI and in the hospital management phase has been described earlier in Sections 6.3.1.6.9.1 and 7.4.3. Through their ability to interfere with ventricular remodeling, thereby attenuating ventricular dilation over time, ACE inhibitors improve clinical outcomes among patients with LV dysfunction (LVEF less than 0.40) after STEMI. The clinical result is a lessened likelihood for development of CHF, recurrent MI, and death. They are also of value in patients without clinical evidence of CHF but with a history of previous MI, in whom they have been shown to reduce cardiovascular mortality, future MI, and cardiac arrest.

These observations, coupled with experience in both the rat model of STEMI (1255) and large randomized clinical trials (585,1256,1257), have established that use of ACE inhibitors begun after a patient has recovered from STEMI improves long-term survival, provided the infarct was large and anterior in location, and results in significant impairment of LV contractility. Specifically, in the SAVE trial, patients took captopril at a mean 11 days after onset of infarction, which resulted in an approximate 20% reduction in mortality (1256). The Acute Infarction Ramipril Efficacy (AIRE) trial, in which patients who had been in clinical heart failure during the first day of their infarct and then were randomly assigned to either ramipril or placebo an average of 5 days after onset of infarction, resulted in significant risk reduction in all-cause mortality (6% ARD; 27% RRR) (1257). Similarly, the TRACE trial, in which patients with LV dysfunction on echocardiogram were randomly assigned to receive either trandolapril or placebo a median of 4 days after onset of infarction, demonstrated a significant reduction in mortality (7.6% ARD; 22% RRR) (1258).

The SOLVD trial evaluated the ACE inhibitor enalapril in 4228 asymptomatic patients with LVEF less than 0.35, 80% of whom had experienced a prior MI (1259). However, randomization was performed considerably later on the average than in the SAVE and AIRE trials. This prevention arm of the SOLVD trial revealed a trend toward improved mortality but not a statistically significant difference (1260). On the other hand, SOLVD did demonstrate a significant risk reduction of 20% for the combined end points of death or development of CHF requiring hospitalization.

In secondary analyses of the initial ACE inhibitor trials, the benefit of treatment appeared to be primarily in patients with anterior infarctions or LVEF below 0.40. However, based on post hoc analysis of the SAVE trial, in which the likelihood of recurrent MI was reduced by approximately 25% in treated patients, studies were initiated to determine the benefits of ACE inhibitor therapy among patients with known CHD but no clinical evidence for CHF (1261). Compelling evidence now supports the broad chronic use of ACE inhibitors after STEMI. The HOPE trial evaluated the effect of long-term (4 to 6 years) ACE inhibition therapy with ramipril 10 mg per day in 9297 high-risk patients, 2480 of whom were women. Fifty-two percent of the patients had a history of MI, and in 10%, the MI was within 1 year. Overall, there was a highly significant reduction in the combined end point of MI, stroke, and all-cause cardiovascular mortality (3.8% ARD; 22% RRR; p less than 0.001). Significant reductions were seen for each individual component of the primary end point: MI 2.4% ARD, RRR 20%; stroke 1.5% ARD, RRR 32%; and death of any cause 1.8% ARD, RRR 16%. Importantly, the study was performed in patients who were not known to have low ejection fraction or heart failure. The European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) evaluated the use of the ACE inhibitor perindopril given 8 mg per day among 13 655 patients (age range 26 to 89 years, mean 60 years) with known CHD but no history of clinical heart failure (1262). Nearly two thirds (64%) of the patients had a history of previous MI (more than 3 months before screening). After a mean follow-up of 4.2 years, treatment with perindopril was associated with a significant reduction (2% ARD; 20% RRR; p equals 0.0003) in the combined end point of nonfatal MI, cardiovascular mortality and resuscitated cardiac arrest. The benefit began to appear at 1 year and gradually progressed throughout the trial. Patients in EUROPA all had CHD but a lower risk than those in HOPE, in which the enrollment age was 55 years or older and 39% had diabetes. In EUROPA, nearly one third of the patients were younger than 55 years, and fewer had diabetes and hypertension. Moreover, the benefits of ACE inhibitor therapy with perindopril were observed in spite of relatively high use of other secondary prevention therapies such as platelet inhibitors (91%), lipid-lowering medications (69%), and beta-blockers (63%). Given the results of the HOPE trial and the secondary analysis from the initial ACE inhibitor trials, ACE inhibitor therapy is recommended for all patients after STEMI unless otherwise contraindicated.

The results of the VALIANT study evaluating the ARB valsartan are discussed in Section 7.4.3. The series of CHARM studies (Candesartan in Heart Failure Assessment in Reduction of Mortality, although focusing on the evaluation of the ARB candesartan in patients with chronic heart failure, provides information that can be extrapolated to the long-term management of the STEMI patient, because 50% to 60% of the patients studied had ischemic heart disease as the cause of heart failure. In patients with symptomatic heart failure and LVEF 0.40 or less who were intolerant of ACE inhibitors (CHARM-Alternative trial), candesartan (target dose 32 mg once daily) was more effective than placebo in preventing cardiovascular death or hospital admission for heart failure (7% ARD; 23% RRR) (1263). In patients with symptomatic heart failure and LVEF 0.40 or less who were being treated with an ACE inhibitor (CHARM-Added trial), candesartan (target dose 32 mg) was more effective than placebo in preventing cardiovascular death or hospital admission for heart failure (4% ARD; 15% RRR) (1264). In

patients with symptomatic heart failure but with a preserved LVEF (greater than 0.40; CHARM-Preserved trial), candesartan had no impact on cardiovascular death compared with placebo but was associated with a trend toward fewer admissions for heart failure (1265).

Given the extensive randomized trial and routine clinical experience with ACE inhibitors, they remain the logical first agent for inhibition of the renin-angiotensin-aldosterone system in the long-term management of patients with STEMI (726). The ARBs valsartan and candesartan should be administered over the long term to patients with STEMI with symptomatic heart failure who are intolerant of ACE inhibitors. As described in Section 7.4.3, the choice between an ACE inhibitor and an ARB in patients who are tolerant of ACE inhibitors over the long term will vary with individual physician and patient preference, as well as cost and anticipated side-effect profile (726).

The results of the most relevant clinical trials testing combinations of ACE inhibitors and ARBs have subtly different but clinically relevant results. Whereas the CHARM-Added (1264) trial demonstrated a reduction in the combined end point of heart failure hospitalization and death over ACE inhibition alone, the VALIANT study (725) reported that the combination of captopril and valsartan was equivalent to either alone, but with a greater number of adverse effects. Thus, when combination ACE inhibition and angiotensin receptor blockade is considered, the preferred ARB is candesartan. Although there is evidence that the combination of an ACE inhibitor and an aldosterone inhibitor is effective at reducing mortality and is well tolerated in patients with a serum creatinine less than or equal to 2.5 mg/dL and serum potassium concentration less than or equal to 5.0 mmol/L (see Section 7.4.3), much less experience exists with the combination of an ARB and an aldosterone inhibitor (24% of 2028 patients in the CHARM-Alternative trial) and the triple combination of an ACE inhibitor, ARB, and an aldosterone antagonist (17% of 2548 patients in the CHARM-Added trial) (1263,1264).

The combination of an ACE inhibitor and an ARB (valsartan 20 mg orally per day initially, titrated up to 160 mg orally twice per day, or candesartan 4 to 8 mg orally per day initially, titrated up to 32 mg orally per day) or an ACE inhibitor and an aldosterone inhibitor may be considered for the long-term management of patients with STEMI with symptomatic heart failure and ejection fraction less than 0.40, provided the serum creatinine is less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women and serum potassium concentration is less than or equal to 5.0 mEq/L. (See Sections 7.4.3 and 7.6.4.)

7.12.7. Beta-Blockers

Class I

1. **All patients after STEMI except those at low risk (normal or near-normal ventricular function, successful reperfusion, absence of significant ventricular arrhythmias) and those with contraindications should receive beta-blocker therapy. Treatment should begin within a few days of the event, if not initiated acutely, and continue indefinitely. *(Level of Evidence: A)***
2. **Patients 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 after STEMI who have no contraindications to that class of medications. *(Level of Evidence: A)*

The use of beta-blockers in the early phase of STEMI and in hospital management is reviewed in Sections 6.3.1.6 and 7.4.1. The benefits of beta-blocker therapy in patients without contraindications have been demonstrated with or without reperfusion, initiated early or later in the clinical course, and for all age groups. The greatest mortality benefit is seen in patients with the greatest baseline risk: those with impaired ventricular function or ventricular arrhythmias and those who do not undergo reperfusion (1266,1267). The benefits of beta-blocker therapy for secondary prevention are well established (717,1012). In patients with moderate or severe LV failure, beta-blocker therapy should be administered with a gradual titration scheme (1268). Long-term beta-blocker therapy should be administered to survivors of STEMI who have subsequently undergone revascularization, because there is evidence of a mortality benefit from their use despite revascularization either with CABG surgery or with PCI (1269).

Given these well-documented benefits, it is disturbing that this therapy continues to be underused, especially in high-risk groups such as the elderly (1270). Beta-blockers should be prescribed for all high-risk patients provided no contraindications are present. In patients with an extremely good prognosis (first STEMI, good ventricular function, no angina, negative stress test, and no complex ventricular ectopy), the effect of beta-blockers on survival will be less (1271). However, beta-blockers are often prescribed for these patients to minimize the likelihood of recurrent ischemic symptoms and to help control surges of heart rate and blood pressure with exertion.

Although relative contraindications may once have been thought to preclude the use of beta-blockers in some patients, evidence now suggests that the benefits of beta-blockers in reducing reinfarctions and mortality may actually outweigh the risks, even in patients with mild asthma not currently active, insulin-dependent diabetes mellitus, chronic obstructive pulmonary disease, severe peripheral vascular disease, PR interval greater than 0.24 seconds, and moderate LV failure. The use of beta-blockers in such patients requires monitoring to be certain that adverse events do not occur (1270,1272,1273).

Some controversy exists as to how long patients should be treated (1274). Data from large trials suggest that therapy should be continued for at least 2 to 3 years (851,1275). Thereafter, if the beta-blocker is well tolerated, such therapy

should probably be continued in most patients, although data are lacking.

7.12.8. Blood Pressure Control

Class I

1. **Blood pressure should be treated with drug therapy to less than 140/90 mm Hg and to less than 130/80 mm Hg for patients with diabetes or chronic kidney disease. *(Level of Evidence: B)***
2. **Lifestyle modification (weight control, dietary changes, physical activity, and sodium restriction) should be initiated in all patients with blood pressure greater than or equal to 120/80 mm Hg. *(Level of Evidence: B)***

Class IIb

A target goal of 120/80 mm Hg for post-STEMI patients may be reasonable. *(Level of Evidence: C)*

Class III

Short-acting dihydropyridine calcium channel blocking agents should not be used for the treatment of hypertension. *(Level of Evidence: B)*

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (1276) recommends that patients be treated after MI with ACE inhibitors, beta-blockers, and, if necessary, aldosterone antagonists to a target blood pressure of less than 140/90 mm Hg, or less than 130/80 mm Hg for those with chronic kidney disease or diabetes (1276). Most patients will require 2 or more drugs to reach goal, and when the blood pressure is greater than 20/10 mm Hg above goal, 2 drugs should usually be used from the outset. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (1277) demonstrated that an antihypertensive regimen based on a thiazide diuretic was equal to an ACE inhibitor– or long-acting calcium channel blocker–based regimen in coronary outcomes and superior in other outcomes (CHF, stroke). Most patients received a beta-blocker in addition to the thiazide.

Beta-blockers reduce the risk for subsequent MI or sudden cardiac death and are indicated in all patients after STEMI absent specific contraindications; they may be especially efficacious in patients with CHF. In general, beta-blockers without intrinsic sympathomimetic activity should be used. Beta-blockers are sufficiently important that they should be withheld only for high-grade heart block, demonstrated intolerance, or other absolute contraindications. Most patients with asthma are able to tolerate cardioselective beta-blockers (1278). Because of the demonstrated effectiveness of thiazide diuretics for reducing adverse outcomes, they should be strongly considered when a second or third agent is needed. ACE inhibitors (or ARBs if ACE inhibitors are not tolerated) should be used long term for the treatment of hypertension when LV dysfunction is present to prevent subsequent heart failure and mortality (1279). ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic and nondiabetic kidney disease but should be given with careful attention to the development of hyperkalemia (1276). Long-acting calcium channel blockers may be used if other agents are not tolerated or are not sufficient to reach blood pressure goal. Short-acting calcium antagonists should not be used (636).

JNC-7 emphasizes the importance of lifestyle modifications for all patients with blood pressure of 120/80 mm Hg or greater (1276). These modifications include: weight reduction if overweight or obese, consumption of a diet rich in fruits and vegetables and low in total fat and saturated fat, and reduction of sodium to no more than 2.4 g/d (1276).

7.12.9. Diabetes Management

Class I

Hypoglycemic therapy should be initiated to achieve HbA1C less than 7%. *(Level of Evidence: B)*

Class III

Thiazolidinediones should not be used in patients recovering from STEMI who have New York Heart Association class III or IV heart failure. *(Level of Evidence: B)*

Tight glucose control in diabetics during and after STEMI has been shown to lower acute and 1-year mortality rates (602). Tight glucose control, defined as an HbA1C of less than 7.0%, reduces microvascular disease and is strongly recommended, although further data are needed regarding its specific benefits for macrovascular disease (1280). Control of hyperglycemia has been shown to reduce diabetes-related events, including MI (2.7% absolute reduction; 16% relative reduction), for patients aged 25 to 65 years with newly detected type 2 diabetes but without symptomatic macrovascular disease (1280).

Thiazolidinediones are frequently used as monotherapy or in combination with other oral hypoglycemic agents, insulin, and diet for control of diabetes. Although thiazolidinediones may be helpful in combating insulin resistance and thereby may improve vascular, neurohormonal, and myocardial function, their use may also be associated with fluid retention and an increase in LV preload (1281) that is resistant to diuretics. Therefore, thiazolidinediones should not be used in patients recovering from STEMI who have New York Heart Association class III or IV heart failure (1281,1282).

7.12.10. Hormone Therapy

Class III

1. **Hormone therapy with estrogen plus progestin should not be given de novo to postmenopausal women after STEMI for secondary prevention of coronary events. *(Level of Evidence: A)***
2. **Postmenopausal women who are already taking estrogen plus progestin at the time of a STEMI should not continue hormone therapy. However, women who are**

beyond 1 to 2 years after initiation of hormone therapy who wish to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing a greater risk of cardiovascular events. Hormone therapy should not be continued while patients are on bedrest in the hospital. ***(Level of Evidence: B)***

Landmark randomized clinical trials have provided firm evidence that combination estrogen and progestin replacement therapy should not be used for either primary or secondary prevention of cardiovascular disease in women. Observational studies (1283,1284) have been interpreted as indicating that oral unopposed estrogen is effective in primary prevention of cardiovascular disease. Confounding factors such as compliance (1285), selection bias, and baseline health in these studies make it difficult to be certain of the effect of estrogen therapy alone.

Clinical trials have shown that estrogen given alone or in combination with progestin improves the lipid profile and lowers fibrinogen (1286). Favorable effects of estrogen on the lipid profile would theoretically be expected to produce a favorable result in preventing coronary atherosclerosis. However, combining estrogen with a progestin (hormone therapy) (1287) reduces the potential beneficial effect of estrogen given alone on the lipid profile. In addition, hormone therapy has been reported to increase high-sensitivity C-reactive protein levels (1288).

The first large-scale, randomized, double-blind, placebo-controlled trial that addressed the question of estrogen plus progestin for secondary prevention of CHD in postmenopausal women was published by Hulley et al. (1287) for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Contrary to conventional wisdom and several observational studies (1289-1292), this trial of 3763 postmenopausal women with established coronary disease and an average age of 66.7 years found no reduction in overall risk for nonfatal MI or coronary death, nor any other cardiovascular outcome, during an average of 4.1 years of follow-up when comparing 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (1380 patients) to placebo (1383 patients).

This lack of an overall effect occurred despite a net 11% lower LDL-C level and a 10% higher HDL-C level in the group given hormone therapy compared with the placebo group (p less than 0.001). There was a statistically significant time trend, however, with more primary coronary events in the hormone therapy group than in the placebo group in year 1 and fewer in years 4 and 5. However, the latter was due to nonfatal MI, because CHD deaths were similar in the 2 groups in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 versus 12; RR 2.89; 95% CI 1.50 to 5.58) and gallbladder disease (84 versus 62; RR 1.38; 95% CI 1.00 to 1.92). HERS II extended the unblinded follow-up of the HERS cohort (93% of survivors) for an additional 2.7 years (total 6.8 years of observation) (1293). The lower rates of CHD in the hormone therapy–assigned women in the latter years of HERS did not persist during additional observation. Hormone therapy did not reduce CHD events after 6.8 years. The Estrogen Replacement and Atherosclerosis (ERA) trial showed no effect of estrogen alone or estrogen plus progesterone on the progression of coronary artery disease, despite favorable effects on lipids (1292). A small randomized controlled trial of transdermal estradiol for women after non–ST-elevation acute coronary syndrome showed no benefit, with a trend toward excess events (1294). The Women's Health Initiative (WHI) Hormone Trial (HT) includes a group of women who have had hysterectomies (10 000) and receive unopposed estrogen and women with intact uteruses who receive the same estrogen plus progestin used in HERS (1295-1297). Participants are not required to have CHD and are generally younger than those in the HERS cohort. The HT trial completed its enrollment of 27 348 women and planned to report the results of the trial in 2005 after 9 years of treatment. However, the data and safety monitoring board recommended early termination of the combination of estrogen and progestin trial after 5.2 years' average follow-up on the basis of an excess of invasive breast cancer (HR 1.26, 1.00 to 1.59) and CHD (HR 1.29, 1.02 to 1.63), stroke (HR 1.41, 1.07 to 1.85), and pulmonary embolism (HR 2.13, 1.39 to 3.25) in study participants receiving active hormone replacement therapy. The estrogen-only versus placebo trial of the WHI study is continuing. In the Women's Angiographic Vitamin and Estrogen (WAVE) Trial, assignment to conjugated equine estrogen, with or without progestin, resulted in worsening of angiographic and clinical outcomes (1298,1299). In a similar trial, WELL-HART (Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial), there was no effect of 17-beta-estradiol, with or without progestin, on angiographic progression of disease (1299). Of note, no randomized trial enrolled women within 3 to 6 months of an acute coronary syndrome.

Inherited thrombophilias may increase the risk of thrombosis due to estrogen (1300). However, none have been clearly identified that would permit screening and exclusion of women at excess risk. The role of selective estrogen receptor modulators is yet to be defined (1291,1293,1301). On the basis of WHI, HERS, and HERS II, postmenopausal women should not receive combination estrogen and progestin therapy for primary or secondary prevention of CHD (1287,1293,1297). It is recommended that hormone therapy be discontinued for women who have STEMI (1297). However, women who are beyond 1 to 2 years after initiation of HT and wish to continue it for another compelling indication should weigh the risks and benefits, recognizing a greater risk of cardiovascular events. Hormone therapy should not be continued while patients are on bedrest in the hospital.

7.12.11. Warfarin Therapy

Class I

1. **Warfarin should be given to aspirin-allergic post-STEMI patients with indications for anticoagulation as follows:**
   a. **Without stent implanted (INR 2.5 to 3.5) *(Level of Evidence: B)*.**
   b. **With stent implanted and clopidogrel 75 mg/d administered concurrently (INR 2.0 to 3.0) *(Level of Evidence: C)***
2. **Warfarin (INR 2.5 to 3.5) is a useful alternative to clopidogrel in aspirin-allergic patients after STEMI who do not have a stent implanted. *(Level of Evidence: B)***
3. **Warfarin (INR 2.0 to 3.0) should be prescribed for post-STEMI patients with either persistent or paroxysmal AF. *(Level of Evidence: A)***
4. **In post-STEMI patients with LV thrombus noted on an imaging study, warfarin should be prescribed for at least 3 months *(Level of Evidence: B)* and indefinitely in patients without an increased risk of bleeding. *(Level of Evidence: C)***
5. **Warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2.0 to 3.0) in combination with aspirin (75 to 162 mg) should be prescribed in post-STEMI patients who have no stent implanted and who have indications for anticoagulation. *(Level of Evidence: B)***

Class IIa

1. **In post-STEMI patients less than 75 years of age without specific indications for anticoagulation who can have their level of anticoagulation monitored reliably, warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2.0 to 3.0) in combination with aspirin (75 to 162 mg) can be useful for secondary prevention. *(Level of Evidence: B)***
2. **It is reasonable to prescribe warfarin to post-STEMI patients with LV dysfunction and extensive regional wall-motion abnormalities. *(Level of Evidence: A)***

Class IIb

Warfarin may be considered in patients with severe LV dysfunction, with or without CHF. *(Level of Evidence: C)*

The indications for long-term anticoagulation after STEMI remain controversial and are evolving. Although the use of warfarin has been demonstrated to be cost-effective compared with standard therapy without aspirin, the superior safety, efficacy, and cost-effectiveness of aspirin has made it the antithrombotic agent of choice for secondary prevention (Figure 37; Table 33) (1248,1249,1302-1305). Two trials failed to demonstrate a statistically significant reduction in the combined end points of death, reinfarction, or stroke using a regimen of low-dose aspirin in combination with low-dose warfarin (INR less than 2) (1306,1307).

Several trials (1247-1249,1303-1305) have examined the use of moderate- and high-intensity warfarin in secondary prevention. Two of these trials, WARIS II and APRICOT (Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis) II, were STEMI specific. In the APRICOT II trial (1249), patients less than 75 years old with STEMI received UFH, aspirin, and fibrinolytic therapy. Those who achieved TIMI 3 flow were randomized to aspirin alone (80 mg) or warfarin (INR 2 to 3) plus 80 mg of aspirin. The combined group had fewer reocclusions (15% versus 28%; p less than 0.02) and a significant reduction in the combined end points of death, MI, and revascularization (20% ARD; 23% RRR; p less than 0.01) (Figure 37; Table 33) (1248,1249,1303-1305).

The WARIS II study of 3630 subjects compared high-intensity warfarin (INR 2.8 to 4.2) alone, medium-intensity warfarin (INR 2 to 2.5) plus aspirin (75 mg), and aspirin alone (160 mg) (1303). Patients were less than 75 years of age. At follow-up in 4 years, the combined group had a lower risk for an event (death, nonfatal reinfarction, thromboembolic cerebral stroke) (3.3% ARD; 29% RRR; p equals 0.03) and the high-intensity warfarin group had a lower risk (5% ARD; 19% RRR; p equals 0.001) than the aspirin group. There was no survival difference, and the benefit resulted from a reduction in nonfatal MI and nonfatal thromboembolic stroke. Bleeding was more common in the warfarin groups, and approximately 35% of patients discontinued warfarin therapy (Figure 37; Table 33) (1248,1249,1303-1305).

In ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) II, aspirin (81 mg) (1248) was compared with high-intensity anticoagulation (INR 3 to 4) and with medium-intensity warfarin (INR 2 to 2.5) plus aspirin (1248) for secondary prevention in 999 subjects (1308). Significantly fewer patients in the high-dose warfarin and the combined regimen had death, MI, or stroke than in the aspirin group (5%, 5%, and 9%, respectively). Major bleeding was low in all groups. Minor bleeding was higher in the combined group. However, almost 20% of the warfarin and combined group discontinued therapy, and only about 40% remained in the therapeutic range.

Although in these studies, medium-intensity warfarin plus low-dose aspirin clearly reduced the rate of nonfatal reinfarctions and nonfatal strokes, this was achieved at the expense of increased bleeding and significant dropout rates. Patients over 75 years of age have not been studied adequately. Therefore, the Writing Committee wishes to make no definitive recommendation in this age group at this time. The high rate of discontinuation and the relatively large number of patients not on target remain problematic. Unless there are indications for anticoagulation, at this time, the Writing Committee reserves its current level IIa recommendation for those patients under 75 years of age and not at risk of bleeding who are at high risk for reinfarction or thromboembolic events and who can be monitored reliably. For patients in whom anticoagulation is indicated, warfarin (INR 2.5 to 3.5) or medium-intensity warfarin (INR 2.0 to 3.0) plus aspirin

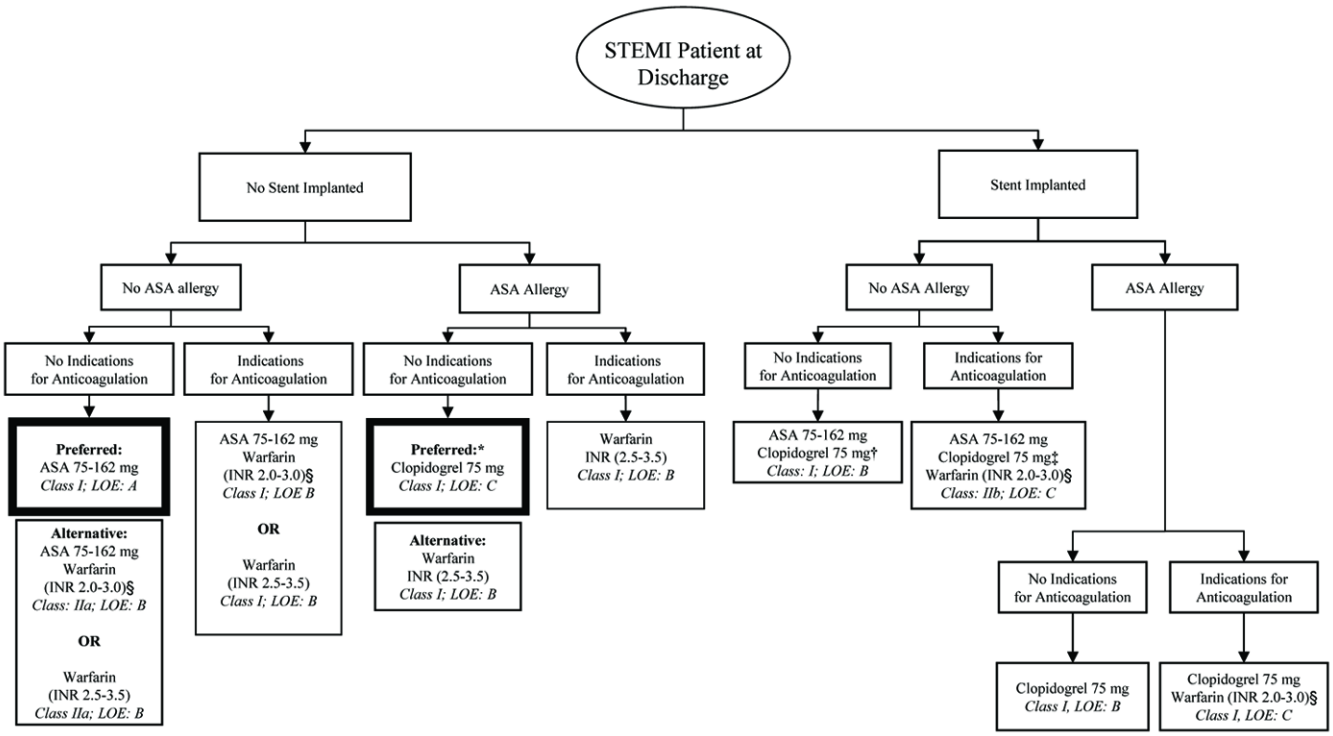

Figure 37. Long-term antithrombotic therapy at hospital discharge after ST-elevation myocardial infarction (STEMI). ASA = aspirin; INR = international normalized ratio; LOE = level of evidence. *Clopidogrel is preferred over warfarin because of increased risk of bleeding and low patient compliance in 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 2 antiplatelet agents. Continue aspirin 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 to 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 who can be monitored reliably.

(75 to 162 mg) may be used for secondary prevention. When warfarin is used in combination with aspirin, an INR of 2.0 to 3.0 is acceptable with tight control, but the lower end of the range is preferable (Figure 37).

The use of clopidogrel and direct thrombin inhibitors in STEMI remains to be studied more thoroughly. Although definitive data are not available, the consensus of this Writing Committee is that clopidogrel is preferred over warfarin in aspirin-intolerant patients for secondary prevention unless reasons for anticoagulation are present (Figure 37). Patients who have undergone stenting may need to take aspirin, clopidogrel, and warfarin (INR 2.0 to 3.0) if anticoagulation is indicated (i.e., AF, LV thrombus, cerebral emboli, or extensive regional wall-motion abnormality) (Figure 37). In this situation, the Writing Committee believes that clopidogrel may be stopped 1 month after a bare metal stent is implanted and several months after a drug-eluting stent is implanted (3 months after sirolimus and 6 months after paclitaxel) because of the potential risk of bleeding with warfarin and the antiplatelet agents (1309,1310). (See Section 7.12.5.)

The previous ACC/AHA guidelines strongly recommended the use of oral anticoagulants with an INR of 2.0 to 3.0 in patients with a ventricular mural thrombus or a large akinetic region of the LV for at least 3 months. In a meta-analysis and other observational studies (1311-1317), patients with LV thrombus after STEMI had better outcomes and fewer cerebral emboli when they underwent anticoagulation with heparin and warfarin. Despite the absence of controlled studies, late thromboembolism was reduced in postinfarction patients with LV aneurysm treated with warfarin in a number of studies (1314-1316). A cohort analysis from the SOLVD trial (1318) demonstrated that warfarin use was associated with improved survival and reduced morbidity in post-MI patients with LV dysfunction. Other studies and a Cochrane review suggest that we be cautious in recommending warfarin for this indication alone (1017,1319). Warfarin is indicated in patients with persistent AF after STEMI, given the results of multiple trials in other patients with AF (955,958).

7.12.12. Physical Activity

Class I

1. **On the basis of assessment of risk, ideally with an exercise test to guide the prescription, all patients recovering from STEMI should be encouraged to exercise for a minimum of 30 minutes, preferably daily but at least 3 or 4 times per week (walking, jogging, cycling, or other aerobic activity), supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work). *(Level of Evidence: B)***

Table 33. Aspirin Versus Warfarin Therapy After ST-Elevation Myocardial Infarction (STEMI)

Study (Ref)	Study Design	Drugs Used	ASA	2nd Arm	3rd Arm	Patients	Endpoints	RESULTS ASA alone %	RESULTS Warfarin Alone %	RESULTS ASA + Warfarin %
STEMI-SPECIFIC TRIALS										
WARIS II (1303)	Randomized Open label N=3630 FU=Mean 4 yrs.	ASA monotherapy vs. Warfarin monotherapy vs. Warfarin + ASA	160 mg daily	Dosed to target INR 2.8-4.2	Dosed to target INR 2.0-2.5 + ASA 75 mg daily	Age less than 75 yrs. Hospitalized for acute MI **% STEMI=71.8**	Death, nonfatal reinfarction, or thromboembolic stroke Major, nonfatal bleeding (P less than 0.001)	20 0.17	16.7 (P=0.03 vs. ASA) 0.68	15 (P=0.001 vs. ASA) 0.57
APRICOT II (1249)	Randomized Open label N=308 FU= 3 mo.	ASA monotherapy vs. Warfarin + ASA	If TIMI 3 post 48 hr UFH then 160 mg initially and then 80 mg daily	Dosed to target INR 2-3 if TIMI 3 post 48 hr UFH + 160 mg initially and then 80 mg daily	N/A	Age less than or equal to 76 yrs. Acute STEMI less than or equal to 6 hrs. prior to thrombolytic Tx. **% STEMI=100**	Reoocclusion (TIMI 2 or less) (P less than 0.02) Total occlusion (TIMI 0-1) (P less than 0.02) Revascularization (P less than 0.01) Reinfarction (P less than 0.05) Event-free survival rate* (P less than 0.01) Bleeding (TIMI major and minor) (P=NS)	28 20 31 8 66 3	N/A	15 9 13 2 86 5
TRIALS NOT SPECIFIC TO STEMI										
ASPECT II (1248)	Randomized Open label N=999 FU=26 mo.	ASA monotherapy vs. Warfarin monotherapy vs. Warfarin + ASA	80 mg daily	Dosed to target INR 3-4	Dosed to target INR 2-2.5 + ASA 80 mg daily	Acute MI or UA within preceding 8 wks.	Death, MI, or stroke (P=0.0479) Major Bleeding Minor Bleeding (P less than 0.0001) Almost 20% of the warfarin and combined group discontinued therapy; 40% in therapeutic range	9 1 5	5 1 8	5 2 15
CHAMP (1304)	Randomized Open label N=5059 FU=Median 2.7 yrs.	ASA monotherapy vs. Warfarin + ASA	162 mg daily	Dosed to target INR 1.5-2.5 + 81 mg ASA daily	N/A	Acute MI within preceding 14 days prior to enrollment	Death (P=0.76) Recurrent MI (P=0.78) Stroke (P=0.52) Major Bleeding (P less than 0.001)	17.3 13.1 3.5 0.72†	N/A	17.6 13.3 3.1 1.2†
CARS (1305)	Randomized Blinded N=8803 FU=33 mo. Median=14 mo.	ASA monotherapy vs. Warfarin 1mg + ASA	160 mg daily (avg INR @ Wk 4= 1.02)	1mg + 80 mg ASA (avg INR @ Wk 4=1.05)	N/A	Age 21-85 yrs. (82% less than 70 yrs) MI 3-21 days (mean 9.6 days) prior to enrollment	Ischemic Stroke (P=0.0534)	0.6	N/A	1.1

FU = follow-up; ASA = aspirin; INR = international normalized ratio; N/A = not applicable; Tx = treatment; MI = myocardial infarction.
*Events are death, revascularization, or reinfarction.
†Reported as number of events per 100 person-years of follow-up.

2. **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)***

Federal guidelines recommend that all Americans strive for at least 30 minutes of moderate physical activity most days of the week, preferably daily (1320). The 30 minutes can be spread out over 2 or 3 segments during the day. For post-patients with STEMI, daily walking can be encouraged immediately after discharge. Physical activity is important in efforts to lose weight because it increases energy expenditure and plays an integral role in weight maintenance. Physical activity reduces symptoms in patients with cardiovascular disease and improves other cardiovascular disease risk factors. Beyond the instructions for daily exercise, patients require specific instruction on those strenuous activities (e.g., heavy lifting, climbing stairs, yard work, household activities) that are permissible and those they should avoid. As emphasized by the US Public Health Service, comprehensive cardiac rehabilitation services include long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling (1184). These programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients. Enrollment in a cardiac rehabilitation program after discharge may enhance patient education and compliance with the medical regimen and assist with the implementation of a regular exercise program (1183,1322-1324). In addition to aerobic training, mild- to moderate-resistance training is also recommended. This can be started 2 to 4 weeks after aerobic training has begun (1325).

7.12.13. Antioxidants

Class III

Antioxidant vitamins such as vitamin E and/or vitamin C supplements should not be prescribed to patients recovering from STEMI to prevent cardiovascular disease. ***(Level of Evidence: A)***

Earlier observational data from epidemiological studies suggested that an increased intake of lipid-soluble antioxidant vitamins (vitamin E and beta-carotene) is associated with reduced rates of cardiovascular events, including STEMI (1326-1328). In support of these data, one randomized placebo-control study of vitamin E treatment in 2002 patients with documented coronary disease indicated a reduction in nonfatal MI (27% ARD; 77% RRR) but no effect on cardiovascular death or overall mortality (1329). However, a midstudy change in the vitamin E dose and some imbalance in the use of beta-adrenoceptor blockers in subjects receiving vitamin E make interpretation of that study problematic. A prospective cohort study of more than 34 000 postmenopausal women suggested that an increase in dietary vitamin E but not supplemental vitamin E was associated with decreased cardiovascular risk (1330). In a randomized trial involving 11 324 patients surviving recent (less than 3 months) MI, patients were assigned to treatment with the following: vitamin E (300 mg daily; n equals 2830); n-3 polyunsaturated fatty acids (1 g daily; n equals 2836); both (n equals 2830); or neither (n equals 2828) for 3.5 years. Treatment with n-3 polyunsaturated fatty acids but not vitamin E significantly lowered the relative risk of the primary end point (death, nonfatal MI, or stroke) by 10% (p equals 0.048) (1331). Thus, although dietary supplementation with n-3 polyunsaturated fatty acids may have clinical benefits for patients after STEMI, this trial failed to demonstrate a treatment benefit for vitamin E. With regard to beta-carotene, several prospective studies have convincingly shown a lack of beneficial effect on cardiovascular disease (1332-1334), and 2 studies have indicated an increase in lung cancer with beta-carotene treatment (1332,1333).

There is even less evidence to support the use of water-soluble enzymatic antioxidants for cardiovascular disease. Although one study suggested reduced cardiovascular risk in subjects taking supplemental vitamin C (1335), the majority of other large epidemiological studies have not indicated a benefit (1326-1328). Thus, routine use of vitamin C after STEMI cannot be recommended.

Despite promising experimental studies, recombinant superoxide dismutase failed to reduce infarct size in a well-controlled primary PCI trial (1336). One small study showed a trend for reduced restenosis with vitamin E treatment after coronary angioplasty (restenosis rate 35.5% for treatment group versus 47.5% for placebo group; n equals 100, p equals 0.06) (1337). A larger study evaluating the combination of vitamin E in association with omega-3 fatty acids 2 weeks before elective PCI showed no effect on the restenosis rate (1338).

Thus, there is no convincing evidence to support lipid- or water-soluble antioxidant supplementation in patients after STEMI or in patients with or without established coronary disease (1338a). Because these agents are not harmless, the growing practice of recommending antioxidant supplements in these patients should be discouraged until the results of ongoing, well-controlled studies become available and unequivocally indicate a beneficial effect. An extensive review of this subject has been published (1338).

8. LONG-TERM MANAGEMENT

8.1. 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 the year after hospital discharge. ***(Level of Evidence: A)***

Depression is a common consequence of STEMI, with major depression occurring in 15% to 20% of patients with STEMI and some degree of clinically significant depression occurring in up to half (1339). Most studies have found depression to be a significant independent predictor of post-MI mortality (1340-1345), although others have not (1346,1347). An ancillary follow-up study from the ENRICHD trial (Enhancing Recovery in Coronary Heart Disease) of a subsample of 358 depressed patients with an acute MI compared with 408 nondepressed patients found that the depressed patients were at higher risk for all-cause mortality but not until nearly 12 months after the acute event. Depression did not predict nonfatal recurrent infarction (1348). The excess risk associated with depression soon after STEMI remains significant for a longer time than previously thought, and a dose-response relationship exists between depression and mortality. The level of depression symptoms at the time of STEMI admission is more closely linked to long-term (5-year) survival than the level at 1 year, notably so in patients with moderate to severe levels of depression. Even minimal degrees of depression appear to confer risk, and risk increases with degree of depression as measured on the Beck Depression Inventory (1340). Depression markedly decreases quality of life for post-STEMI patients (1339,1346,1347,1349,1350) and is associated with substantially greater costs (1341). Fatigue does not explain the impact of STEMI in producing depression (1343), nor do infarct size, LV function, or other physiological variables predict the degree of depression (1345,1339). Depression rather than physiological variables predicts failure to return to usual activity and failure of social role resumption after MI (1351). Depressed patients are less likely to complete cardiac rehabilitation and less likely to adhere to important lifestyle changes and medications. (1352,1353).

Treatment of depression with combined cognitive-behavioral therapy and selective serotonin reuptake inhibitors improves outcome in terms of depression symptoms and social function (1350,1354,1355). A double-blind study comparing sertraline and placebo found that sertraline was associated with clinically meaningful improvement in multiple quality-of-life domains in patients hospitalized with acute coronary syndrome (74% of which was acute MI) in the previous month who had recurrent depression (1350). Although one randomized controlled trial showed no reduction in mortality or reinfarction (1355), a reanalysis suggested its follow-up was not long enough to demonstrate effect, and indeed, depression was associated with mortality in that study (1348). Therefore, it appears prudent to assess patients with STEMI for depression during hospitalization and during the first month after STEMI and to intervene and reassess yearly in the first 5 years, as appropriate. There is evidence that the STEMI experience, with its sudden and unexpected onset, dramatic changes in lifestyle, and the additive effort of comorbid life events, is a relatively traumatic event and may produce impaired coping during subsequent ischemic events (1356).

Social integration and social support repeatedly have been shown to influence outcomes after STEMI. Social integration refers to the existence of social ties (e.g., spouse, close family members, or friends) and degree of participation in group activities (e.g., family gatherings, religious affiliations). Social support refers to the actual or perceived receipt of information, materials, and/or emotional support.

Mortality from all causes, including ischemic heart disease, is lower in socially integrated individuals (1357). Recurrent cardiac events are also significantly lower among persons reporting high levels of social integration than among socially isolated persons (1358,1359). When social support was clearly defined and measured and the effect of depression was controlled for, a large prospective trial (1360) demonstrated that support did not directly predict post-MI mortality. However, high levels of support mitigated the effect of depression on post-MI mortality. A randomized controlled trial of a social support and depression management intervention similarly did not demonstrate reduced mortality (1355) but did significantly reduce social isolation.

The most effective social support interventions occur naturally. The quality of the support provided is key; support has been shown to facilitate treatment compliance, but only when policing is minimized (1362). Overprotectiveness and withholding of information or worries, either of the patient by family members or vice versa, is associated with worse outcomes (1363,1364). Telephone follow-up, cardiac rehabilitation, or other group events can be effective methods of support for socially isolated individuals (1365).

Anxiety is prevalent among hospitalized patients with STEMI but declines relatively rapidly after discharge to levels typical of the general medical population (1366). Anxiety is predictive of in-hospital recurrent ischemia and arrhythmias after MI (707), and physicians' and nurses' subjective judgments of patient anxiety are not accurate compared with measurement on validated scales (709). At least one randomized controlled trial demonstrates that in-hospital anxiety and depression can be reduced by a structured nursing support intervention (714), and secondary analysis of a longer-term trial suggests that both long-term psychosocial distress and health outcomes may benefit (1367). Anxiety should be assessed at the time of hospital discharge of patients hospitalized for STEMI. A number of studies have examined psychological intervention programs designed to help post-MI patients' psychosocial and emotional adjustment. Two large post-MI programs (1341,1368) failed to achieve positive outcomes on psychological factors or prognosis. Some have observed that the type of approach used with patients recovering from MI varies in terms of its association with anxiety reduction (1367,1369). Nevertheless, one meta-analysis reported that the addition of psychosocial interventions to standard treatment resulted in significantly less depression,

anxiety, morbidity, and mortality (1370). Psychosocial interventions in cardiac rehabilitation were found in another review to improve the odds for mortality and recurrence of nonfatal MI, but not necessarily with regard to females and older participants (1369). A secondary analysis of a longer-term trial suggests that both long-term psychosocial prognosis and health outcomes may improve in patients whose psychological status improves (1367).

8.2. Cardiac Rehabilitation

Class I

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)*

Cardiac rehabilitation programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients (1184,1371,1372). Cardiac rehabilitation is a comprehensive long-term program that involves medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling (1184,1373). Cardiac rehabilitation can occur in a variety of settings, including supervised groups in a hospital, physician's office, or community facility. In clinically stable lower-risk patients, rehabilitation can be undertaken independently, with regular guidance from a cardiac rehabilitation healthcare professional (1184). The exercise can be supervised or unsupervised and can involve a stationary bicycle, treadmill, calisthenics, walking, or jogging. Home exercise training programs have been shown to be beneficial in certain low-risk patient groups. They offer the advantages of convenience and low cost but lack the valuable elements of education and group interaction (1374).

The pooled effect estimate for total mortality for the exercise-only intervention demonstrated a reduction in all-cause mortality (random effects model OR 0.73 [0.54, 0.98]) compared with usual care. Comprehensive cardiac rehabilitation reduced all-cause mortality but to a lesser degree (OR 0.87 [0.71, 1.05]). Neither of the interventions had any effect on the occurrence of nonfatal MI. The authors concluded that exercise-based cardiac rehabilitation appeared to be effective in reducing cardiac deaths but that it was still unclear whether an exercise-only or a comprehensive cardiac rehabilitation intervention was more beneficial. The population studied was predominantly male, middle-aged, and low risk. The authors suggested that those who may have benefited from the intervention were excluded owing to age, gender, or comorbidity. The authors cautioned that the results were of limited reliability because the quality of reporting in the studies was generally poor, and there were high losses to follow-up (1373).

Cardiac rehabilitation comprising exercise training and education, counseling, and behavioral interventions yielded improvements in exercise tolerance with no significant cardiovascular complications, improvements in symptoms (decreased anginal pain and improved symptoms of heart failure such as shortness of breath and fatigue), and improvements in blood lipid levels; reduced cigarette smoking in conjunction with a smoking cessation program; decreased stress; and improved psychosocial well-being (1184). In addition to reductions in total cholesterol and LDL-C, increases in HDL levels have been reported (1197).

Existing community studies reveal that fewer than one third of patients with STEMI receive information or counseling about cardiac rehabilitation before being discharged from the hospital (1184,1375). Only 16% of patients in a study of 5 hospitals in 2 Michigan communities were referred to a cardiac rehabilitation program at discharge, and only 26% of the patients later interviewed in the community reported actual participation in such a program. However, 54% of the patients referred at discharge did participate at the time of their follow-up interview (1375). Physician referral (to a cardiologist/cardiac surgeon) was the most powerful predictor of patient participation in a cardiac rehabilitation program.

In a longitudinal study of the use of inpatient cardiac rehabilitation in 5204 Worcester, MA, residents hospitalized with MI in 7 1-year periods between 1986 and 1997, patients not referred to inpatient cardiac rehabilitation were less likely to be prescribed effective cardiac medications and to undergo risk factor modification counseling before discharge (1376).

Patient reasons for nonparticipation and noncompliance include affordability of service, possible insurance coverage, social support from a spouse or other caregiver, gender-specific attitudes, patient-specific internal factors such as anxiety or poor motivation, and logistical and financial constraints, or a combination of these factors (1375,1377). Women and the elderly have been reported to be referred less frequently to cardiac rehabilitation programs, even though they have been reported to derive benefit (1378-1380).

8.3. 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 patients' list of current medications should be re-evaluated 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 (Figure 36). 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 (Figure 32). *(Level of Evidence: C)***

4. **The healthcare provider should review and emphasize the principles of secondary prevention with the patient and family members (Table 32) (68). *(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 MET values for various activities are provided as a resource (Table 34). *(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. **It is reasonable that patients be referred to a structured cardiac rehabilitation program after hospital discharge. (*Level of Evidence: C)***

A caring and supportive doctor-patient relationship is vital to the well-being of the survivor and their families. It is common practice to see these patients 3 to 6 weeks after hospital discharge to assess their progress.

The physician should listen to the concerns of their patients and their patients' families and respond flexibly. Future appointments should be scheduled and should reflect the goals set for each individual patient in accordance with their needs and current guidelines.

8.4. Return to Work and Disability

Return-to-work rates, which currently range from 63% (1381) to 94% (1382), are difficult to influence because they are confounded by factors such as job satisfaction, financial stability, and company policies (1383). In PAMI-II, a study of primary PTCA in low-risk patients with STEMI (i.e., age less than 70 years, ejection fraction greater than 0.45, 1- or 2-vessel disease, and good PTCA result), patients were encouraged to return to work at 2 weeks. The actual timing of return to work was not reported, but no adverse events occurred as a result of this strategy (1384).

Disability. There is some evidence that a cardiac rehabilitation program after STEMI contributes to reduction of mortality and improved physical and emotional well-being (see Section 8.2). Patients whose expectations for return to work were addressed in rehabilitation returned to work at a significantly faster rate than the control group in a prospective study (1385).

A low level of depressive symptoms before STEMI increases the odds of recovery of functional status (1386). Patients with high pre-STEMI functional independence measurement have shorter length of stay and greater likelihood of discharge to home (1387). Pre-STEMI peak aerobic capacity and depression score are the best independent predictors of post-STEMI physical function. Women tend to have lower physical function scores than men of similar age, depression score, and comorbidity. Resting LVEF is not a predictor of physical function score.

Patients' cardiac functional states are not a strong predictor of their probability of returning to work. Diabetes, older age, Q-wave MI, and preinfarction angina are associated with failure to resume full employment (1388). However, psychological variables such as trust, job security, patient feelings about disability, expectations of recovery by both physician and patient, and degree of somatizing are more predictive (1389,1390). Physical requirements of the job play a role as well (1388,1390).

To aid occupational physicians in making return-to-work decisions, Froom et al. (1388) studied the incidence of post-MI events at 1, 2, 4, 6, 9, and 12 months. The events included cardiac death, recurrent infarction, CHF, and unstable angina. They found that the incidence of events reached a low steady state at 10 weeks.

Return to work can be determined by employer regulations rather than by the patient's medical condition. It behooves the physician to provide data to prove that the patient's job does not impose a prohibitive risk for a cardiac event. An example is the case of the Canadian bus drivers reported by Kavanagh et al. (1391). The patients were evaluated with a stress test. The physician and technologist studied the drivers at work and showed that the cardiac stress values during driving were only half of the average values obtained in the stress laboratory. The calculated risk of sudden cardiovascular incidence causing injury or death to passengers, other road users, and the drivers in the first year after recovery from an MI was 1 in 50 000 driving years. The bus drivers were allowed to return to work after they satisfied the Canadian Cardiovascular Society guidelines.

Women have entered the job market and are faced not only with the gender difference but in procedure difference and mortality. Covinsky et al. (1392) performed a mail survey study of patients with MIs. Three months after discharge, women reported worse physical and mental health and were more likely to work less than before the MI. Similarly, women were less likely to return to work than men.

Table 34. Energy Levels Required to Perform Some Common Activities

Less Than 3 METs	3-5 METs	5-7 METs	7-9 METs	More Than 9 METs
Self-care				
Washing	Cleaning windows	Easy digging in garden	Sawing wood	Carrying loads upstairs
Shaving	Raking	Level hand lawn mowing	Heavy shoveling	(objects more than 90 lb)
Dressing	Power lawn mowing	Climbing stairs (slowly)	Climbing stairs (moderate speed)	Climbing stairs (quickly)
Desk work	Bed making/stripping	Carrying objects (30-60 lb)	Carrying objects (60-90 lb)	Shoveling heavy snow
Washing dishes	Carrying objects (15-30 lb)	Digging vigorously		
Driving auto				
Light housekeeping				
Occupational				
Sitting (clerical/ assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Lumber jack
Typing	Auto repair	Shoveling dirt		Heavy labor
Desk work	Light welding/carpentry	Sawing wood		
Standing (store clerk)		Operating pneumatic tools		
Recreational				
Golf (cart)	Dancing (social)	Badminton (competitive)	Canoeing	Handball
Knitting	Golf (walking)	Tennis (singles)	Mountain climbing	Squash
Hand sewing	Sailing	Snow skiing (downhill)	Paddle ball	Ski touring
	Tennis (doubles)	Light backpacking		Vigorous basketball
	Volleyball (6 persons)	Basketball		
		Football		
		Stream fishing		
Physical conditioning				
Walking (2 mph)	Level walking (3-4 mph)	Level walking (4.5-5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6-8 mph)	Bicycling (9-10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
			Bicycling (12 mph)	

Modified from Haskell. Rehabilitation of the coronary patient. In: Wenger and Hellerstein, eds. Design & implementation of cardiac conditioning program. New York, NY: Churchill Livingstone; 1978, Table 9.2, p. 147 (1393).

The current aggressive interventional treatment of STEMI will have an impact on mortality, morbidity, and hospital length of stay (696). It remains to be determined whether earlier improvement in cardiac condition after STEMI will have an effect on the rate of return to work because of the multiple noncardiac factors that influence disability and return to work.

8.5. Other Activities

In patients who desire to return to physically demanding activities early, the safety of activity can be determined by comparing performance on a graded exercise test with the MET level required for the desired activity. Table 34 presents energy levels, expressed in METs, required to perform a variety of common activities (1393). This and similar tables can be helpful in translating a patient's performance on a graded exercise test into daily activities that may be undertaken with reasonable safety.

The physician should provide explicit advice about when to return to previous levels of physical activity, sexual activity, and employment. Daily walking can be encouraged immediately (1394). In stable patients without complications (class I), sexual activity with the usual partner can be resumed within 1 week to 10 days. Driving can begin 1 week after discharge if the patient is judged to be in compliance with individual state laws. Each state's Department of Motor Vehicles or its equivalent has mandated certain criteria, which vary from state to state and must be met before operation of a motor vehicle after serious illness (1395) These include such caveats as the need to be accompanied and to avoid stressful circumstances such as rush hour, inclement weather, night driving, heavy traffic, and high speeds. For patients who have experienced a complicated STEMI (one that required CPR or was accompanied by hypotension, serious arrhythmias, high-degree block, or CHF), driving should be delayed 2 to 3 weeks after symptoms have resolved.

Most commercial aircraft are pressurized to 7500 to 8000 feet and therefore could cause hypoxia due to the reduced alveolar oxygen tension. The maximum level of pressurization is limited to 8000 feet (2440 meters) by Federal Aviation Administration regulation (1396). Therefore, air travel within the first 2 weeks of STEMI should be undertaken only if there is no angina or dyspnea at rest or fear of flying. The individual must have a companion, carry nitroglycerin, and request airport transportation to avoid rushing (personal communication, R.P. Gardner, PhD, November 2002). Air travel for cardiac patients should gradually become safer. Availability of an emergency medical kit and AED has been mandated for April 12, 2004, (1398) in all aircraft that carry at least approximately 30 passengers and have at least 1 flight attendant.

STAFF

American College of Cardiology

Christine W. McEntee, Chief Executive Officer

Katherine D. Doermann, Specialist, Knowledge Development

Kristina N. Petrie, MS, Research Analyst, Knowledge Development

American Heart Association

M. Cass Wheeler, Chief Executive Officer

Rose Marie Robertson, MD, FACC, FAHA, Chief Science Officer

Kathryn A. Taubert, PhD, FAHA, Vice President, Science and Medicine

APPENDIX 1. ACC/AHA Committee to Revise the 1999 Guidelines for Management of Acute Myocardial Infarction—Relationships With Industry

Committee Member Name	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant
Dr. Elliott M. Antman	Aventis Bayer Biosite Boehringer Mannheim Bristol-Myers Squibb British Biotech Centor Cor/Millennium Corvas Dade Genentech Lilly Merck Pfizer Sunol	None	None	Aventis
Dr. Daniel T. Anbe	None	None	None	None
Dr. Paul W. Armstrong	Boehringer Ingelheim Eli Lilly Hoffmann-LaRoche Millennium Proctor & Gamble Sanofi	Aventis Hoffman-LaRoche	Medicure, Inc.	Aventis Hoffmann-LaRoche Medicure, Inc.
Dr. Eric R. Bates	Aventis Centocor Cor/Millennium Eli Lilly Genentech The Medicines Co. Merck	None	None	None
Dr. Lee A. Green	None	None	None	None
Ms. Mary Hand	None	None	None	None
Dr. Judith S. Hochman	Merck Aventis Cor/Millennium Guidant Lilly			Daichii Proctor & Gamble
Dr. Harlan M. Krumholz	None	None	None	Astra-Zeneca BMS/Sanofi CVT
Dr. Frederick G. Kushner	Aginamoto Co. Andrx Labs Atherogenics, Inc. Boehringer-Ingelheim Medtronic Novartis Rorer Schering-Plough	Bristol-Myers Squibb Merck Pfizer Reliant	Abbott Labs Baxter Guidant Medtronic Merck Pfizer	Millennium, Inc.

Continued on next page

APPENDIX 1. *Continued*

Committee Member Name	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant
Dr. Gervasio A. Lamas	Astra Zeneca Bayer Centocor Bristol-Myers Squibb Guidant Lilly Medtronic Novartis Schering	None	None	None
Dr. Charles J. Mullany	Cardiogenesis	None	None	None
Dr. Joseph P. Ornato	Genentech Meridian Medical Corp. Wyeth	None	None	Bristol-Myers-Squibb Genentech HP/Agilent Medtronic Meridian Medical Corp. Philips PhysioControl/Scios Revivant Corp. Wyeth
Dr. David L. Pearle	None	GlaxoSmithKlein Novartis Pfizer	None	None
Dr. Michael A. Sloan	Abbott Labs Astra Zeneca Bristol-Myers Squibb Genentech Novo-Nordisk	Boehringer-Ingelheim Dupont Genentech Merck Nicolet-EME	None	None
Dr. Sidney C. Smith, Jr.	Merck Pfizer	None	Medtronic	None

This table represents the actual or potential relationships of committee members with industry that were reported orally at the initial writing committee meeting in January 2002 and updated in conjunction with all meetings and conference calls of the writing committee. It does not reflect any actual or potential relationships at the time of publication.

APPENDIX 2. External Peer Reviewers for the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction*

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. John W. Hirshfeld, Jr.	Official Reviewer – ACCF Board of Trustees	None	None	None	None
Dr. W. Barton Campbell	Official Reviewer – ACCF Board of Governors	None	None	None	None
Dr. Joseph S. Alpert	Official Reviewer – ACC/AHA Task Force on Practice Guidelines	None	None	None	None
Dr. Scott Grundy	Official Reviewer – AHA	Abbott Laboratories Astra Zeneca Bristol-Myers Squibb GlaxoSmithKline Kos Pharmaceuticals McNeil Pharmaceuticals Merck Pfizer Veterans Affairs	Abbott Laboratories Astra Zeneca Bristol-Myers Squibb Cooper Aerobics Center Kos Pharmaceuticals McNeil Pharmaceuticals Merck Pfizer Tularik, Inc.	None	None
Dr. L. Kristin Newby	Official Reviewer – AHA; AHA Committee on Acute Cardiac Care	Bristol-Myers Squibb Dade-Behring Millennium Novartis Roche Diagnostics Roche Pharmaceuticals Sanofi Schering-Plough Research Institute	Biosite Bristol-Myers Squibb-Sanofi Ischemia Technologies Institute	None	None
Dr. E. Magnus Ohman	Official Reviewer – AHA; AHA Committee on Acute Cardiac Care	Aventis Berlex Bristol-Myers Squibb Merck Millennium Pfizer Sanofi	None	Medtronic	None
Dr. Deborah Allen	Organizational Reviewer – American Academy of Family Physicians	None	None	None	None
Dr. Peter Bogaty	Organizational Reviewer – Canadian Cardiovascular Society	Merck Pfizer	Abbott Laboratories	Merck	None
Dr. Jennifer Adgey	Content Reviewer – Individual Review	None	None	None	None
Dr. Jeffrey Anderson	Content Reviewer – ACC/AHA Task Force on Practice Guidelines	None	Johnson & Johnson/Merck Merck Merck/Schering Plough	None	Alteon Merck Johnson & Johnson/Merck
Dr. Jean Barbey	Content Reviewer – Pharmacological Review	None	None	None	None
Dr. Eugene Braunwald	Content Reviewer – ACC/AHA 2002 Guideline Update for Management of Unstable Angina	None	None	None	None

*Participation in the peer review process does not imply endorsement of the document.
†Names are listed in alphabetical order within each category of review.

Continued on next page

APPENDIX 2. *Continued**

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Robert Califf	Content Reviewer – ACC/AHA 2002 Guideline Update for Management of Unstable Angina	Accumetrics Actelion Ajinomoto Alsius Amgen Astra Hassle Aventis Biomarin Biosite Boston Scientific Bracco Bristol-Myers Squibb Cambridge Heart Cardiodynamics Centocor Chase Medical Chiron Coagulation Diagnostics Corcept Corgentech Critline Dade Behring Daiichi Datascope Devco Elan Pharmaceuticals Enzon Esai Geneceutics Genentech GlaxoSmithKline Guidant Guilford Pharmaceuticals Harvard Health Care Hemosol InfraReDx Intracel IOMED Lincare Medicure Medivance Medtronic Foundation Merck Millennium NABI Novartis Ortho Biotech Otsuka Parke Davis Pfizer Pharmacia/Upjohn Pheromone Science Proctor and Gamble Promethesus Quanam Salix Sanofi Spectranetics St. Jude Medical Synaptic The Medicines Company Theravance Vesicor Vicuron Wyeth Ayerst Yamanouchi	Aventis Bristol-Myers Squibb Conceptis GlaxoSmithKline Merck Millennium Novartis Ortho Biotech Paraxel Pennside Partners Pfizer Pharmacia/Upjohn Pharsight Schering Plough Wyeth Ayerst	None	GlaxoSmithKline Pfizer

*Participation in the peer review process does not imply endorsement of the document.
†Names are listed in alphabetical order within each category of review.

Continued on next page

APPENDIX 2. *Continued**

Peer Reviewer† Name	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Kanu Chatterjee	Content Reviewer – ACC/AHA 2002 Guideline Update for Management of Chronic Stable Angina	None	Astra Zeneca CV Therapeutics Bristol-Myers Squibb Merck Novartis Pfizer	None	None
Dr. James Cleeman	Content Reviewer – Individual Review	None	None	None	None
Dr. Stephen Ellis	Content Reviewer – ACCF Clinical Data Standards for Acute Coronary Syndromes	Medtronic	None	None	Cordis Guidant Boston Scientific
Dr. Nathan Every	Content Reviewer – ACCF Clinical Data Standards for Acute Coronary Syndromes	Genentech	None	None	None
Dr. Daniel Fintel	Content Reviewer – Individual Review	None	Merck Aventis Sanofi	None	Aventis
Dr. Valentin Fuster	Content Reviewer – ACC/AHA Task Force on Practice Guidelines	Cordis GlaxoSmithKline Schering AG	None	None	GlaxoSmithKline
Dr. Bernard Gersh	Content Reviewer – Individual Review	None	None	None	None–
Dr. Raymond Gibbons	Content Reviewer – ACCF Cardiovascular Imaging Committee	Alsius Corp Boehringer Ingelheim (pending) Boston Scientific (pending) Innercool Therapies King Pharm Medtronic Radiant Medical Ther Ox Wyeth-Ayerst	None	None	Boehringer Ingelheim Biostream (pending) CV Therapeutics DOV Pharmaceuticals GlaxoSmithKline Hawaii Biotech King Pharm Medicure
Dr. W. Brian Gibler	Content Reviewer – AHA Committee on Cardiac Care	Bristol-Myers Squibb Acute Millennium/Schering Plough	None	None	None
Dr. A. Daniel Glassman	Content Reviewer – Individual Review	None	None	None	None
Dr. Gabriel Gregoratos	Content Reviewer – ACC/AHA Task Force on Practice Guidelines	None	None	None	GlaxoSmithKline
Dr. Cindy Grines	Content Reviewer – Individual Review	Amersham Health Aventis Berlex Eli-Lilly Esperion Therapeutics GlaxoSmithKline Guidant Innercool Therapies Johnson & Johnson Otsuka Pfizer SCIMED	None	None	Aventis Innercool Therapies Guidant The Medicines Company Pfizer
Dr. Timothy Henry	Content Reviewer – ACCF Emergency Cardiac Care Committee	Anges Aventis BMS Berlex Boston Scientific Cordis Genentech Genzyme The Medicines Company Medtronic Millennium	None	None	None
Dr. L. David Hillis	Content Reviewer – ACC/AHA Guidelines Update for Coronary Artery Bypass Graft Surgery (in progress)	None	None	None	None

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†Names are listed in alphabetical order within each category of review.

Continued on next page

APPENDIX 2. *Continued**

Peer Reviewer Name†	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Loren Hiratzka	Content Reviewer – ACC/AHA Task Force on Practice Guidelines	None	None	None	None
Dr. David Holmes	Content Reviewer – ACCF Clinical Competence Statement on Interventional Training Procedures	None	None	None	None
Dr. Alan Jaffe	Content Reviewer – Individual Review	Beckman-Coulter Dade-Behring Roche	None	None	Abbott Laboratories Aventis Beckman Dade-Behring Diadexus Ortho Pfizer Roche Sensera
Dr. Desmond Julian	Content Reviewer – Individual Review	None	None	None	AstraZeneca Aventis Eli Lilly GlaxoSmithKline Merck Novartis Pfizer Servier
Dr. Carlos Kase	Content Reviewer – Neurological Review	None	None	None	None
Dr. Dean Kereiakes	Content Reviewer – ACC/AHA 2002 Guideline Update for Management of Unstable Angina	None	None	None	None
Dr. J. Ward Kennedy	Content Reviewer – ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention (in progress)	None	None	None	None
Dr. Peter Libby	Content Reviewer – ACCF Peripheral Vascular Disease Committee	Astra Zeneca Bayer Bristol-Myers Squibb Merck Novartis Pfizer Sankyo SmithKline Beecham	Astra Zeneca Bayer Bristol-Myers Squibb Merck Novartis Pfizer	None	Astra Zeneca Avant Immunotherapeutics Bayer Bristol-Myers Squibb Interleukin Genetics Merck Millennium Novartis Pfizer Pierre Fabre Sankyo Sanofi Schering-Plough SmithKline Beecham Volcano Therapeutics
Dr. A. Michael Lincoff	Content Reviewer – Individual Review	Eli Lilly Centocor The Medicines Company	None	None	None
Dr. Kathleen McCauley	Content Reviewer – Individual Review	None	None	None	None

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Continued on next page

APPENDIX 2. *Continued**

Peer Reviewer† Name	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. George McKendall	Content Reviewer – ACCF Board of Governors ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None
Dr. Richard Pasternak	Content Reviewer – ACC/AHA 2002 Guideline Update for Management of Chronic Stable Angina	None	Bristol-Myers Squibb/Sanofi Merck Merck/Schering-Plough Kos Pfizer	None	Astra Zeneca Bristol-Myers Squibb/Sanofi Johnson & Johnson-Merck Kos Merck Pfizer Health Solutions
Dr. Marc Pfeffer	Content Reviewer – ACCF Hypertensive Diseases Committee	Astra Zeneca Aventis Bristol-Myers Squibb Genzyme Mitsubishi Pharma Corp Novartis Pfizer	Astra Zeneca Aventis Bristol-Myers Squibb Genzyme Mitsubishi Pharma Corp Novartis Pfizer		Ortho Biotech
Dr. Charles Pollack	Content Reviewer – Individual Review	Aventis Sanofi	Aventis Bristol-Myers Squibb Key ACS Millennium Scios		Aventis Key ACS
Dr. Barbara Riegel	Content Reviewer – Individual Review	None	None	None	None
Dr. Rose Marie Robertson	Content Reviewer – Individual Review	None	None	None	Merck (spouse)
Dr. Richard Russell	Content Reviewer – ACC/AHA/ASNC 2003 Guideline Update for Radionuclide Imaging	None	None	None	None
Dr. Thomas Ryan	Content Reviewer – ACC/AHA Guidelines for Management of Patients with Acute Myocardial Infarction	None	None	Abbott Labs Amgen Cardinal Health Care King Pharm	GenVec
Dr. Cathy A Sila	Content Reviewer – Neurological Review	None	None	None	Centocor Paion Bristol-Myers/Sanofi Squibb
Dr. Burton Sobel	Content Reviewer – Individual Review	None	None	None	None

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication.
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APPENDIX 2. *Continued**

Peer Reviewer† Name	Representation	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. John Stratton	Content Reviewer – Individual Review	None	None	None	None
Dr. Frans Van de Werf	Content Reviewer – ACCF Clinical Data Standards for Acute Coronary Syndromes	Aventis Boehringer Ingelheim Genentech Menarini Novartis Servier	Aventis Boehringer Ingelheim Genentech Menarini Novartis Servier	Aventis Boehringer Ingelheim Genentech Menarini Novartis Servier	Aventis Boehringer Ingelheim Genentech Menarini Novartis Servier
Dr. Nanette Wenger	Content Reviewer – Individual Review	Astra Zeneca Bristol-Myers Squibb Eli Lilly	Aventis Bristol-Myers Squibb Eli Lilly Merck Pfizer Wyeth-Ayerst	None	Aventis Bristol-Myers Squibb Merck Pfizer Women First Healthcare, Inc.
Dr. Harvey White	Content Reviewer – Individual Review	None	None	None	The Medicines Company
Dr. Clyde Yancy	Content Reviewer – ACC/AHA Guideline Update for Heart Failure (in progress)	None	Scios	None	GlaxoSmithKline

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication.
*Participation in the peer review process does not imply endorsement of the document.
†Names are listed in alphabetical order within each category of review.

APPENDIX 3. ABBREVIATIONS

AAFP = American Academy of Family Physicians
ACC = American College of Cardiology
ACE = angiotensin converting enzyme
ACEP = American College of Emergency Physicians
ACLS = advanced cardiac life support
AED = automated external defibrillator
AF = atrial fibrillation
AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management
AHA = American Heart Association
ALS = advanced life support
AMI = acute myocardial infarction
AMI-SK = Acute Myocardial Infarction-Streptokinase
ARB = angiotensin receptor blocker
ARD = absolute risk difference
ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Regimen
ATP III = Adult Treatment Panel III report
AV = atrioventricular
AVID = Antiarrhythmics Versus Implantable Defibrillators
bpm = beats per minute
CABG = coronary artery bypass graft surgery
CAPRICORN = Carvedilol Post-infarct Survival Controlled Evaluation
CAPRIE = Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events
CAPTIM = Comparison of Primary Angioplasty and Prehospital Thrombolysis in the Acute Phase of Myocardial Infarction
CARE = Cholesterol And Recurrent Events
CCP = Cooperative Cardiovascular Project
CCS = Canadian Cardiovascular Society
CCU = coronary care unit
CHD = coronary heart disease
CHF = congestive heart failure
CI = confidence interval
CK = creatine kinase
C-PORT = Cardiovascular Patient Outcomes Research Team
CPR = cardiopulmonary resuscitation
CT = computed tomography
CURE = Clopidogrel in Unstable angina to prevent Recurrent Events
DANAMI = DANish multicenter Trial in Acute Myocardial Infarction
DRS = Diltiazem Reinfarction Study
DVT = deep venous thrombosis
ECG = electrocardiogram
ECMO = extracorporeal membrane oxygenation
ED = emergency department
EMS = emergency medical services
EMT = emergency medical technician
EP = electrophysiology
EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
GIK = glucose-insulin-potassium
GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GP = glycoprotein
GUSTO = Global Utilization of Strategies To Open occluded arteries
HDL-C = high-density lipoprotein cholesterol
HERO = Hirulog and Early Reperfusion or Occlusion trial
HERS = Heart and Estrogen/Progestin Replacement Study
HOPE = Heart Outcomes Prevention Evaluation
hsCRP = high-sensitivity C-reactive protein
IABP = intra-aortic balloon pump
ICD = implantable cardioverter defibrillator
ICH = intracranial hemorrhage
IMA = internal mammary artery
InTIME = Intravenous nPA for Treatment of Infarcting Myocardium Early
ISIS = International Study of Infarct Survival
IV = intravenous
JNC-7 = Seventh Joint National Committee on High Blood Pressure
LAD = left anterior descending coronary artery
LBBB = left bundle-branch block
LDL-C = low-density lipoprotein cholesterol
LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease
LMWH = low-molecular-weight heparin
LV = left ventricular, left ventricle
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
MADIT = Multicenter Automatic Defibrillator Implantation Trial
MAGIC = Magnesium in Coronaries trial
MDPIT = Multicenter Diltiazem Postinfarction Trial
MET = metabolic equivalent
MI = myocardial infarction
MR = mitral regurgitation
MUSTT = Multicenter Unsustained Tachycardia Trial
NASCET = North American Symptomatic Carotid Endarterectomy Trial
NCEP = National Cholesterol Education Program
NHAAP = National Heart Attack Alert Program

NHLBI = National Heart, Lung, and Blood Institute
NRMI = National Registry of Myocardial Infarction
NS = not significant
NSTEMI = non–ST-elevation myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
PCWP = pulmonary capillary wedge pressure
PH = parenchymal hemorrhage
PRAGUE = PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis
Primary care provider = physician, nurse practitioner, physician assistant
RBBB = right bundle-branch block
REACT = Rapid Early Action for Coronary Treatment
RR = relative risk
RRR = relative risk reduction
RV = right ventricular, right ventricle
SAVE = Survival and Ventricular Enlargement
SCD = sudden cardiac death
SHOCK = SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK?
SPECT = single-photon emission computed tomography
STEMI = ST-elevation myocardial infarction
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TIMI = thrombolysis in myocardial infarction
TIMI 0 = TIMI grade 0 flow, or no perfusion
TIMI 1 = TIMI grade 1 flow, or penetration without perfusion
TIMI 2 = TIMI grade 2 flow, or partial perfusion
TIMI 3 = TIMI grade 3 flow, or complete perfusion
TLC = Therapeutic Lifestyle Changes
tPA = tissue plasminogen activator
TRACE = Trandolapril Cardiac Evaluation
UA = unstable angina
UFH = unfractionated heparin
VALIANT = Valsartan in Acute Myocardial Infarction Trial
VF = ventricular fibrillation
VSR = ventricular septal rupture
VT = ventricular tachycardia
WARIS = Warfarin-Aspirin Reinfarction Study
WHI = Women’s Health Initiative

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