2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions

WRITING COMMITTEE MEMBERS*
Patrick T. O'Gara, MD, FACC, FAHA, *Chair*†;
Frederick G. Kushner, MD, FACC, FAHA, FSCAI, *Vice Chair**†; Deborah D. Ascheim, MD, FACC†;
Donald E. Casey, Jr, MD, MPH, MBA, FACP, FAHA‡; Mina K. Chung, MD, FACC, FAHA*†;
James A. de Lemos, MD, FACC†; Steven M. Ettinger, MD, FACC*§;
James C. Fang, MD, FACC, FAHA†; Francis M. Fesmire, MD, FACEP*‖¶;
Barry A. Franklin, PhD, FAHA†; Christopher B. Granger, MD, FACC, FAHA*†;
Harlan M. Krumholz, MD, SM, FACC, FAHA*†; Jane A. Linderbaum, MS, CNP-BC†;
David A. Morrow, MD, MPH, FACC, FAHA*†; L. Kristin Newby, MD, MHS, FACC, FAHA*†;
Joseph P. Ornato, MD, FACC, FAHA, FACP, FACEP*†; Narith Ou, PharmD†;
Martha J. Radford, MD, FACC, FAHA†; Jacqueline E. Tamis-Holland, MD, FACC†;
Carl L. Tommaso, MD, FACC, FAHA, FSCAI#; Cynthia M. Tracy, MD, FACC, FAHA†;
Y. Joseph Woo, MD, FACC, FAHA†; David X. Zhao, MD, FACC*†

ACCF/AHA TASK FORCE MEMBERS
Jeffrey L. Anderson, MD, FACC, FAHA, *Chair*;
Alice K. Jacobs, MD, FACC, FAHA, *Immediate Past Chair*;
Jonathan L. Halperin, MD, FACC, FAHA, *Chair-Elect*; Nancy M. Albert, PhD, CCNS, CCRN, FAHA;
Ralph G. Brindis, MD, MPH, MACC; Mark A. Creager, MD, FACC, FAHA; David DeMets, PhD;
Robert A. Guyton, MD, FACC, FAHA; Judith S. Hochman, MD, FACC, FAHA;
Richard J. Kovacs, MD, FACC; Frederick G. Kushner, MD, FACC, FAHA**;
E. Magnus Ohman, MD, FACC; William G. Stevenson, MD, FACC, FAHA;
Clyde W. Yancy, MD, FACC, FAHA**

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACCF/AHA representative. ‡ACP representative. §ACCF/AHA Task Force on Practice Guidelines liaison. ‖ACCF/AHA Task Force on Performance Measures liaison. ¶ACEP representative. #SCAI representative. **Former Task Force member during this writing effort.

This document was approved by the American College of Cardiology Foundation Board of Trustees and the American Heart Association Science and Advisory Coordinating Committee in June 2012.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0b013e3182742cf6/-/DC1.

The online-only Comprehensive Relationships Table is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0b013e3182742cf6/-/DC2.

The American Heart Association requests that this document be cited as follows: O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425.

This article has been copublished in the *Journal of the American College of Cardiology*.

(*Circulation*. 2013;127:e362-e425.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e3182742cf6**

Table of Contents

Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist physicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force), charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, directs and oversees this effort. Writing committees are charged with regularly reviewing and evaluating all available evidence to develop balanced, patient-centric recommendations for clinical practice.

Experts in the subject under consideration are selected by the ACCF and AHA to examine subject-specific data and write guidelines in partnership with representatives from other medical organizations and specialty groups. Writing committees are asked to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and outcomes constitute the primary basis for the recommendations contained herein.

In analyzing the data and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force.[1] The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting

Table 1. Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE 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** *No Benefit* or **CLASS III** *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

each recommendation with the weight of evidence ranked as LOE A, B, or C according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the members of the writing committee is the basis for LOE C recommendations and no references are cited. The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR.

A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another are included for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy*

(GDMT) to represent optimal medical therapy as defined by ACCF/AHA guideline-recommended therapies (primarily Class I). This new term, *GDMT*, will be used throughout subsequent guidelines.

Because the ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential influence of different practice patterns and patient populations on the treatment effect and relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. As a result, situations may arise for which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas are identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the members of the writing committee. All writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 1 year before initiation of the writing effort. In December 2009, the ACCF and AHA implemented a new RWI policy that requires the writing committee chair plus a minimum of 50% of the writing committee to have no *relevant* RWI. (Appendix 1 includes the ACCF/AHA definition of *relevance.*) These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee, and members provide updates as changes occur. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the voting members. Members may not draft or vote on any text or recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. In addition, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement. Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of writing committees is supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this activity.

In an effort to maintain relevance at the point of care for practicing physicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust*.[2,3] It is noteworthy that the IOM cited ACCF/AHA practice guidelines as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update or the full-text guideline is revised. Guidelines are official policy of both the ACCF and AHA.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. The current document constitutes a full revision and includes an extensive evidence review, which was conducted through November 2010, with additional selected references added through August 2012. Searches were limited to studies conducted in human subjects and reviews and other evidence pertaining to human subjects; all were published in English. Key search words included but were not limited to: *acute coronary syndromes, percutaneous coronary intervention, coronary artery bypass graft, myocardial infarction, ST-elevation myocardial infarction, coronary stent, revascularization, anticoagulant therapy, antiplatelet*

therapy, antithrombotic therapy, glycoprotein IIb/IIIa inhibitor therapy, pharmacotherapy, proton-pump inhibitor, implantable cardioverter-defibrillator therapy, cardiogenic shock, fibrinolytic therapy, thrombolytic therapy, nitrates, mechanical complications, arrhythmia, angina, chronic stable angina, diabetes, chronic kidney disease, mortality, morbidity, elderly, ethics, and contrast nephropathy. Additional searches cross-referenced these topics with the following subtopics: percutaneous coronary intervention, coronary artery bypass graft, cardiac rehabilitation, and secondary prevention. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline, along with confidence intervals (CI) and data related to the relative treatment effects such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio.

The focus of this guideline is the management of patients with ST-elevation myocardial infarction (STEMI). Updates to the 2004 STEMI guideline were published in 2007 and 2009.[4–6] Particular emphasis is placed on advances in reperfusion therapy, organization of regional systems of care, transfer algorithms, evidence-based antithrombotic and medical therapies, and secondary prevention strategies to optimize patient-centered care. By design, the document is narrower in scope than the 2004 STEMI Guideline, in an attempt to provide a more focused tool for practitioners. References related to management guidelines are provided whenever appropriate, including those pertaining to percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), heart failure (HF), cardiac devices, and secondary prevention.

1.2. Organization of the Writing Committee

The writing committee was composed of experts representing cardiovascular medicine, interventional cardiology, electrophysiology, HF, cardiac surgery, emergency medicine, internal medicine, cardiac rehabilitation, nursing, and pharmacy. The American College of Physicians, American College of Emergency Physicians, and Society for Cardiovascular Angiography and Interventions assigned official representatives.

1.3. Document Review and Approval

This document was reviewed by 2 outside reviewers each nominated by the ACCF and the AHA, as well as 2 reviewers each from the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions and 22 individual content reviewers (including members from the ACCF Interventional Scientific Council and ACCF Surgeons' Scientific Council). All reviewer RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and the AHA and was endorsed by the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions.

2. Background

2.1. Definition and Diagnosis

STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis. Diagnostic ST elevation in the absence of left ventricular (LV) hypertrophy or left bundle-branch block (LBBB) is defined by the European Society of Cardiology/ACCF/AHA/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction as new ST elevation at the J point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads.[7] The majority of patients will evolve ECG evidence of Q-wave infarction. New or presumably new LBBB has been considered a STEMI equivalent. Most cases of LBBB at time of presentation, however, are "not known to be old" because of prior electrocardiogram (ECG) is not available for comparison. New or presumably new LBBB at presentation occurs infrequently, may interfere with ST-elevation analysis, and should not be considered diagnostic of acute myocardial infarction (MI) in isolation.[8] Criteria for ECG diagnosis of acute STEMI in the setting of LBBB have been proposed (see *Online Data Supplement 1*). Baseline ECG abnormalities other than LBBB (eg, paced rhythm, LV hypertrophy, Brugada syndrome) may obscure interpretation. In addition, ST depression in ≥2 precordial leads (V1–V4) may indicate transmural posterior injury; multilead ST depression with coexistent ST elevation in lead aVR has been described in patients with left main or proximal left anterior descending artery occlusion.[9] Rarely, hyperacute T-wave changes may be observed in the very early phase of STEMI, before the development of ST elevation. Transthoracic echocardiography may provide evidence of focal wall motion abnormalities and facilitate triage in patients with ECG findings that are difficult to interpret. If doubt persists, immediate referral for invasive angiography may be necessary to guide therapy in the appropriate clinical context.[10,11] Cardiac troponin is the preferred biomarker for diagnosis of MI.

2.2. Epidemiology

In 2009, approximately 683 000 patients were discharged from US hospitals with a diagnosis of acute coronary syndrome (ACS). Community incidence rates for STEMI have declined over the past decade, whereas those for non–ST-elevation ACS have increased (Figure 1). At present, STEMI comprises approximately 25% to 40% of MI presentations.[12–15] In-hospital (approximately 5% to 6%) and 1-year (approximately 7% to 18%) mortality rates from STEMI also have decreased significantly in association with a substantial increase in the frequency of care that includes GDMT and interventions ("defect-free" care).[13,15–18] In the United States, important regional differences exist in 30-day acute MI hospital mortality and readmission rates for Medicare beneficiaries ≥65 years of age.[19] Understanding the reasons for

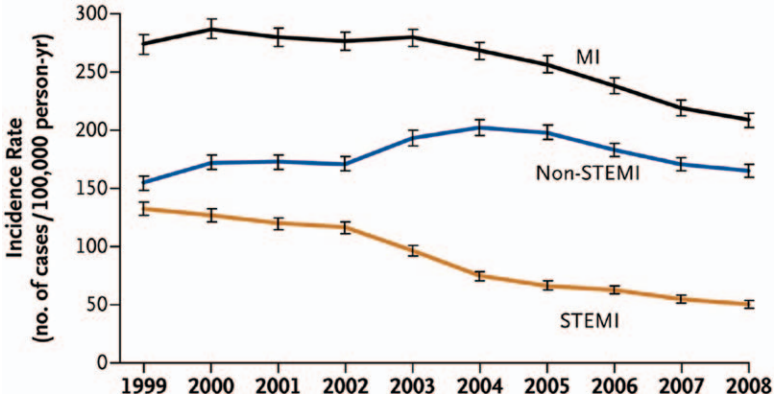

Figure 1. Age- and sex-adjusted incidence rates of acute MI, 1999 to 2008. I bars represent 95% confidence intervals. MI indicates myocardial infarction; STEMI, ST-elevation myocardial infarction. Reprinted with permission from Yeh et al.[14]

such differences may provide opportunities for performance improvement.[20]

Approximately 30% of patients with STEMI are women. Female sex was a strong independent predictor of failure to receive reperfusion therapy among patients who had no contraindications in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry.[21] Compared with men, women included in the NCDR (National Cardiovascular Data Registry) ACTION Registry–GWTG (Get With The Guidelines) presented later after symptom onset, had longer door-to-fibrinolysis and door-to-balloon (or device) (D2B) times, and less often received aspirin or beta blockers within 24 hours of presentation. Women further were characterized by a higher risk for bleeding with antithrombotic therapy, which persisted after consideration of age, weight, blood pressure (BP) at presentation, renal function, baseline hematocrit, and other potential confounders.[22]

Nonwhites represented 13.3% of patients with STEMI at hospitals participating in the ACTION Registry–GWTG in quarters 1 and 2 of 2009.[17] Importantly, disparities in the treatment of racial and ethnic minorities appear to be improving over time.[23] In an assessment of the effects of a statewide program for treatment of STEMI, institution of a coordinated regional approach to triage and management was associated with significant improvements in treatment times that were similar for whites and blacks and for women and men.[23] The writing committee endorses the desirability of collecting and using accurate data on patient race and ethnicity to detect disparities, guide quality improvement initiatives, and strengthen ties to the community.[24]

Approximately 23% of patients with STEMI in the United States have diabetes mellitus,[17] and three quarters of all deaths among patients with diabetes mellitus are related to coronary artery disease.[25,26] Diabetes mellitus is associated with higher short- and long-term mortality after STEMI,[27,28] and in patients with diabetes mellitus, both hyperglycemia and hypoglycemia are associated with worse outcomes.[29] Hyperglycemia at presentation in patients who do not have diabetes mellitus by history has been associated with worse hospital outcomes.[30–34] Myocardial tissue perfusion after restoration of epicardial coronary flow was more impaired among patients with diabetes mellitus ("no-reflow").[28,35,36] Management of patients with diabetes mellitus and STEMI should be the same as for patients without diabetes mellitus, with attention to moderate glycemic control.

The elderly comprise a growing segment of the population and present special challenges for diagnosis and management that may lead to disparities in care and delays in treatment. Additional issues to consider include the risks of antithrombotic and interventional therapies and the appropriate boundaries of care within the context of individual comorbidities, frailty, and advanced-care directives. Clinical trials frequently have limited enrollment of older populations.[37] Treatments that are effective in younger populations usually are indicated in the elderly, with the caveat that the elderly more often have absolute or relative contraindications to their use. Impaired renal function associated with aging requires careful attention to drug dosing.[38,39]

In an analysis of 8578 patients with STEMI from 226 US hospitals participating in the CRUSADE quality improvement initiative from September 2004 to December 2006, 7% of eligible patients did not receive reperfusion therapy.[21] The factor most strongly associated with not providing reperfusion therapy in eligible patients was increasing age. Evidence suggests that even the very elderly have reasonable post-MI outcomes when treated aggressively with reperfusion therapy,[40] though individual circumstances vary.

Both the GWTG Quality Improvement Program and the North Carolina Reperfusion of Acute Myocardial Infarction in Carolina Emergency Department's initiative demonstrated that focused quality improvement efforts and programs designed to systematize care across integrated regional centers can lessen disparities and improve the care of elderly patients with STEMI.[23,41]

Numerous studies have highlighted the fact that patients with chronic kidney disease of all stages less frequently receive guideline-recommended interventions than do patients with normal renal function, despite evidence of benefit from most acute treatments.[42–45] In a project that linked the US Renal Data System database with the NRMI (National Registry of Myocardial Infarction)–3, patients on dialysis had longer prehospital delays, were less often recognized as having an acute MI, and less often had ST elevation or LBBB on initial ECG than patients not on dialysis. Only 45% of eligible patients on dialysis received reperfusion therapy, and only 70% received aspirin on admission. The in-hospital

mortality rate was 21.3% among patients on dialysis, compared with 11.7% for patients with end-stage renal failure not on dialysis. At discharge, only 67% of patients on dialysis were prescribed aspirin, and only 57% were prescribed beta blockers. In the GRACE (Global Registry of Acute Coronary Events) registry, the in-hospital mortality rate was approximately 30% among patients with STEMI or LBBB MI with stage 4 or 5 chronic kidney disease. Both fibrinolysis and primary PCI were associated with higher bleeding rates in patients with severely reduced renal function.[46] Progressive renal dysfunction is a strong predictor of bleeding with antithrombotic therapy, a risk that may reflect intrinsic renal dysfunction and/or failure to adjust or avoid antithrombotic medications that are dependent on renal elimination.[22,47]

2.3. Early Risk Assessment

Global risk assessment provides an opportunity to integrate various patient characteristics into a semiquantitative score that can convey an overall estimate of a patient's prognosis; can dictate the acuity, intensity, and location of care; and can provide the patient and family with a more informed sense of potential outcome. Higher risk scores generally imply that higher-intensity treatments may be appropriate within the context of the patient's health status.

Some of the independent predictors of early death from STEMI include age, Killip class, time to reperfusion, cardiac arrest, tachycardia, hypotension, anterior infarct location, prior infarction, diabetes mellitus, smoking status, renal function, and biomarker findings.[48,49] Whereas the Thrombolysis In Myocardial Infarction (TIMI) risk score was developed specifically in patients with STEMI (http://www.mdcalc.com/timi-risk-score-for-stemi), the GRACE model (http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html) predicts in-hospital and 6-month mortality rate across the spectrum of patients presenting with ACS, including those with ST elevation or ST depression. Risk assessment is a continuous process that should be repeated throughout hospitalization and at time of discharge.

3. Onset of MI

3.1. Patient-Related Delays and Initial Treatment

Patients with STEMI do not seek medical care for approximately 1.5 to 2 hours after symptom onset, and little change in this interval has occurred over the past 10 years.[50,51] Patient delay times are often longer in women, blacks, the elderly, and Medicaid-only recipients and are shorter for Medicare recipients (compared with privately insured patients) and patients who are taken directly to the hospital by emergency medical services (EMS) transport.[52,53] Patients may delay seeking care because their symptoms differ from their preexisting bias that a heart attack should present dramatically with severe, crushing chest pain.[54] Approximately one third of patients with MI experience symptoms other than chest pain.[7] Other reasons for delay in seeking treatment include 1) inappropriate reasoning that symptoms will be self-limited or are not serious[55–57]; 2) attribution of symptoms to other preexisting conditions; 3) fear of embarrassment should symptoms turn out to be a "false alarm"; 4) reluctance to trouble others unless "really sick"[55,57,58]; 5) preconceived stereotypes of who is at risk for a heart attack, an especially common trait among women[59]; 6) lack of knowledge of the importance of rapid action, the benefits of calling EMS or 9-1-1, and the availability of reperfusion therapies[54]; and 7) attempted self-treatment with prescription and/or nonprescription medications.[57] To avoid such delays, healthcare providers should assist patients when possible in making anticipatory plans for timely recognition and response to an acute event. Family members, close friends, or advocates also should be enlisted as reinforcement for rapid action when the patient experiences symptoms of possible STEMI.[60,61] Discussions should include a review of instructions for taking aspirin[62] and nitroglycerin in response to chest pain. Emergency medical dispatchers are trained to instruct patients with possible STEMI symptoms to chew non–enteric-coated aspirin (162 to 325 mg), unless contraindicated, while personnel are en route. If nitroglycerin is prescribed, the patient should be advised to take 1 nitroglycerin dose promptly. If symptoms are unimproved or worsening 5 minutes after 1 dose, the patient should be instructed to call 9-1-1 immediately.

3.2. Mode of Transport to the Hospital

Even though >98% of the US population is covered by 9-1-1 service,[63] patients with STEMI often do not call EMS or 9-1-1 and are not transported to the hospital by ambulance. In a 2011 observational study from the ACTION Registry–GWTG that used data reported from a limited number of predominantly PCI-capable US hospitals, EMS transport was used for only 60% of 37 643 patients with STEMI.[64] Older US surveys reported EMS activation rates of 23% to 53%, with substantial geographic variability.[62,65,66]

Patients with possible ischemic symptoms should be transported to the hospital by ambulance rather than by friends or relatives because 1) 1 in every 300 patients with chest pain transported to the emergency department (ED) by private vehicle suffers cardiac arrest en route[67]; and 2) there is a significant association between arrival at the ED by ambulance and earlier delivery of reperfusion therapy.[64–66,68] In addition, the performance of prehospital ECGs by trained personnel is associated with shorter reperfusion times[69] and lower mortality rates from STEMI. The use of prehospital ECGs, particularly when coupled with communication of STEMI diagnosis and preferential transport to a PCI-capable hospital, has been shown to result in rapid reperfusion times and excellent clinical outcomes.[70–72]

3.3. Patient Education

The AHA and National Institutes of Health "Act in Time to Heart Attack Signs" campaign[73] stresses that patients can increase their chance of surviving STEMI by learning the warning symptoms, filling out a survival plan, and discussing risk reduction with their physician. These materials are available on the National Institutes of Health "Heart Attack" Web page (http://health.nih.gov/topic/HeartAttack/).[74] Healthcare providers should target their educational interventions to patients at increased risk for ACS.[75]

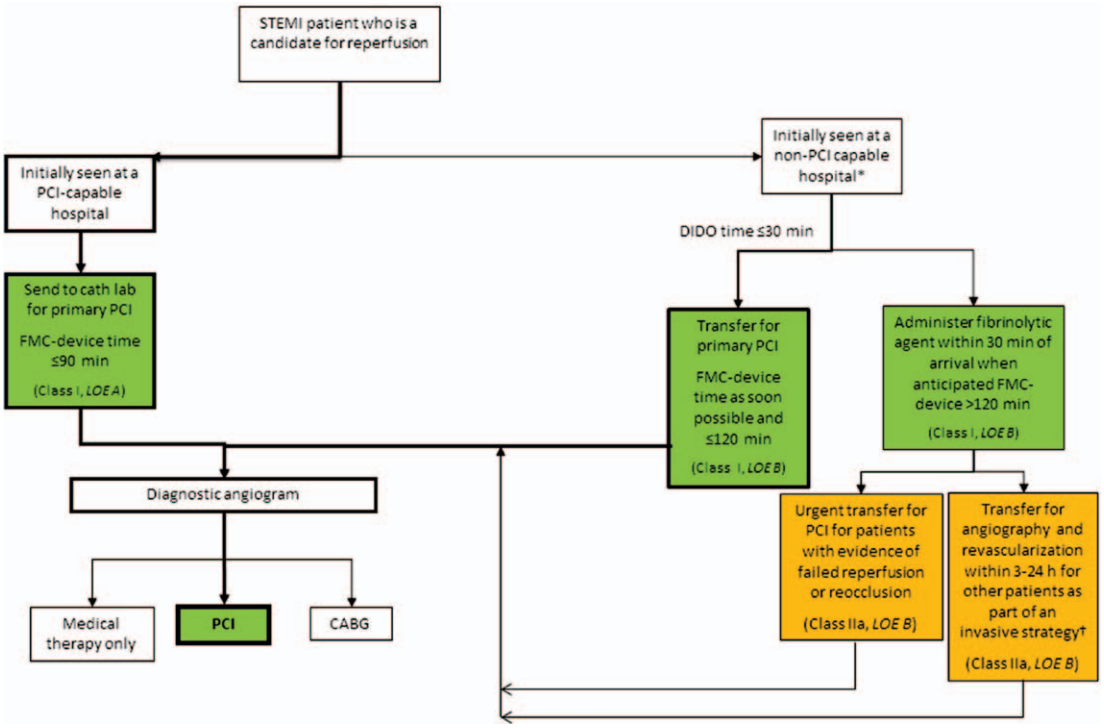

Figure 2. Reperfusion therapy for patients with STEMI. The bold arrows and boxes are the preferred strategies. Performance of PCI is dictated by an anatomically appropriate culprit stenosis. *Patients with cardiogenic shock or severe heart failure initially seen at a non–PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from MI onset (*Class I, LOE: B*). †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. CABG indicates coronary artery bypass graft; DIDO, door-in–door-out, FMC, first medical contact; LOE, Level of Evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

3.4. Community Preparedness and System Goals for Reperfusion Therapy

3.4.1. Regional Systems of STEMI Care, Reperfusion Therapy, and Time-to-Treatment Goals: Recommendations

See Figure 2.

Class I

1. **All communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. Performance can be facilitated by participating in programs such as Mission: Lifeline and the D2B Alliance.[71,76–78] (*Level of Evidence: B*)**
2. **Performance of a 12-lead ECG by EMS personnel at the site of first medical contact (FMC) is recommended in patients with symptoms consistent with STEMI.[70–72,79,80] (*Level of Evidence: B*)**
3. **Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours.[81,82] (*Level of Evidence: A*)**
4. **Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators.[82–84] (*Level of Evidence: A*)**
5. **EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device time system goal of 90 minutes or less.*[70–72] (*Level of Evidence: B*)**
6. **Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non–PCI-capable hospital, with an FMC-to-device time system goal of 120 minutes or less.*[83–86] (*Level of Evidence: B*)**
7. **In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays.[81,87,88] (*Level of Evidence: B*)**
8. **When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival.*[89–93] (*Level of Evidence: B*)**

Class IIa

1. **Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population.[81,94,95] (*Level of Evidence: B*)**

*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.

3.4.1.1. Regional Systems of STEMI Care and Goals for Reperfusion Therapy

Any regional medical system must seek to enable rapid recognition and timely reperfusion of patients with STEMI. System delays to reperfusion are correlated with higher rates of mortality and morbidity.[96–100] Although attention to certain performance metrics, such as D2B, door-to-needle, and door-in–door-out times, have catalyzed important institutional quality improvement efforts, broader initiatives at a systems level are required to reduce total ischemic time, the principal determinant of outcome.[101,102] Questions have been raised about the overreliance on primary PCI for reperfusion, especially in the United States, and the unintended consequences that have evolved as familiarity with fibrinolysis has waned.[101] The writing committee reiterates the principle highlighted in the 2004 ACC/AHA STEMI guideline, namely that "the appropriate and timely use of some form of reperfusion therapy is likely more important than the choice of therapy."[4] Greatest emphasis is to be placed on the delivery of reperfusion therapy to the individual patient as rapidly as possible.

Only a minority of US hospitals are capable of performing primary PCI,[103] and any delay in time to reperfusion (D2B) after hospital arrival is associated with a higher adjusted risk of in-hospital mortality in a continuous, nonlinear fashion.[96] Strict time goals for reperfusion may not always be relevant or possible for patients who have an appropriate reason for delay, including initial uncertainty about diagnosis, the need for evaluation and treatment of other life-threatening conditions (eg, acute respiratory failure, cardiac arrest), delays involving informed consent, and long transport times due to geographic distance or adverse weather. To reduce hospital treatment delays, the ACC initiated the D2B Alliance in 2006 to improve door-to-device times in patients with STEMI.[104] The D2B Alliance goal was for participating PCI-capable hospitals to achieve a D2B time of ≤90 minutes for at least 75% of nontransferred patients with STEMI. The Alliance met this goal by 2008.[105] A longitudinal study of hospitals participating in the NCDR CathPCI Registry demonstrated that patients treated in hospitals that had been enrolled in the D2B Alliance for ≥3 months were significantly more likely to have D2B times of ≤90 minutes than patients treated in nonenrolled hospitals.[105]

In a similar manner, the AHA launched "Mission: Lifeline" in 2007 to improve health system readiness and response to STEMI,[106,107] with a focus on the continuum of care from EMS activation to primary PCI. Patients may present directly by private transport to a PCI-capable hospital, in which case all medical care occurs in a single center responsible for optimizing door-to-device times. For patients who call 9-1-1, direct care begins with FMC, defined as the time at which the EMS provider arrives at the patient's side. EMS personnel should be accountable for obtaining a prehospital ECG, making the diagnosis, activating the system, and deciding whether to transport the patient to a PCI-capable or non–PCI-capable hospital. Consideration should be given to the development of local protocols that allow preregistration and direct transport to the catheterization laboratory of a PCI-capable hospital (bypassing the ED) for patients who do not require emergent stabilization upon arrival. Although "false positives" are a concern when EMS personnel and/or emergency physicians are allowed to activate the cardiac catheterization laboratory, the rate of false activations is relatively low (approximately 15%) and is more than balanced by earlier treatment times for the majority of patients for whom notification is appropriate.[108–114] The concept of what constitutes false activation is evolving.[115,116] For patients who arrive at or are transported by EMS to a non–PCI-capable hospital, a decision about whether to transfer immediately to a PCI-capable hospital or to administer fibrinolytic therapy must be made. Each of these scenarios involves coordination of different elements of the system. On the basis of model systems of STEMI care in the United States and Europe,[77,78,117–121] Mission: Lifeline recommends a multifaceted community-wide approach that involves patient education, improvements in EMS and ED care, establishment of networks of STEMI-referral (non–PCI-capable) and STEMI-receiving (PCI-capable) hospitals, and coordinated advocacy efforts to work with payers and policy makers to implement healthcare system redesign. Detailed information about this program can be found on the AHA website.[122]

Several factors should be considered in selecting the type of reperfusion therapy (Figure 2). For patients with STEMI presenting to a PCI-capable hospital, primary PCI should be accomplished within 90 minutes. For patients presenting to a non–PCI-capable hospital, rapid assessment of 1) the time from onset of symptoms, 2) the risk of complications related to STEMI, 3) the risk of bleeding with fibrinolysis, 4) the presence of shock or severe HF, and 5) the time required for transfer to a PCI-capable hospital must be made and a decision about administration of fibrinolytic therapy reached. Even when interhospital transfer times are short, there may be relative advantages to a strategy of immediate fibrinolytic therapy versus any delay to primary PCI for eligible patients who present within the first 1 to 2 hours after symptom onset.[89,101,123,124]

Several trials have suggested a benefit of transferring patients with STEMI from a non–PCI-capable hospital to a PCI-capable hospital for primary PCI,[83,125] but in many instances, transfer times are prolonged and delays may be unavoidable. In the NCDR,[126,127] only 10% of transferred patients were treated within 90 minutes of initial presentation, with a median first door-to-device time of 149 minutes. In many communities, a significant percentage of patients with STEMI who present initially to a non–PCI-capable hospital cannot physically be transferred to a PCI-capable hospital and achieve an FMC-to-device time treatment goal of ≤90 minutes. DANAMI-2 (Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction) showed that a reperfusion strategy involving the transfer of patients with STEMI from a non–PCI-capable hospital to a PCI-capable hospital for primary PCI was superior to the use of fibrinolysis at the referring hospital, driven primarily by a reduction in the rate of reinfarction in the primary PCI–treated group.[83,85] In this study, the average first door-to-device time delay was approximately 110 minutes.[85] Shorter system delays were associated with a reduced mortality rate for both

fibrinolysis- and primary PCI–treated patients. In an analysis of approximately 19 000 propensity score–matched patients with STEMI from NRMI-2, -3, -4, and -5, when delays related to transfer for primary PCI exceeded 120 minutes from FMC, the survival advantage of primary PCI over fibrinolysis was negated. Delays beyond 120 minutes occurred in nearly half the patients in the analysis.[100] Thus, interhospital transfer to a PCI-capable hospital is the recommended triage strategy if primary PCI consistently can be performed within 120 minutes of FMC. Fibrinolytic therapy, in the absence of contraindications to its use, should be administered within 30 minutes of first door arrival when this 120-minute time goal cannot be met. Transfer delays can occur at multiple levels and for varied reasons.[128] Efforts are needed to reduce the time delay between arrival to and transfer from a non–PCI-capable hospital (ie, door-in–door-out). Among a subset of 14 821 patients in the NCDR ACTION–GWTG registry, the median door-in–door-out time was 68 minutes (interquartile range, 43 to 120 minutes). A door-in–door-out time ≤30 minutes, achieved in only 11% of patients, was associated with shorter delays to reperfusion and a lower in-hospital mortality rate.[129] Because estimation of treatment times for patients can be inaccurate, the decision to transfer for primary PCI should be based on actual, historical times achieved within the regional system, with quality assurance programs to ensure that such goals are consistently met. A reasonable goal would be that 90% of patients should meet the 120-minute time-to-treatment standard to achieve performance standards.

Several triage and transfer strategies have been tested and are discussed further in Section 5.3. The term *facilitated PCI* was used previously to describe a strategy of full- or half-dose fibrinolysis, with or without administration of a glycoprotein (GP) IIb/IIIa receptor antagonist, with immediate transfer for planned PCI within 90 to 120 minutes. Two large studies failed to show a net clinical benefit with this strategy.[130,131] The term *rescue PCI* refers to the transfer for PCI of patients who demonstrate findings of failed reperfusion with fibrinolysis.[103,130] The term *pharmacoinvasive strategy* refers to the administration of fibrinolytic therapy either in the prehospital setting or at a non–PCI-capable hospital, followed by immediate transfer to a PCI-capable hospital for early coronary angiography and PCI when appropriate. Patients with STEMI who are best suited for immediate interhospital transfer for primary PCI without fibrinolysis are those patients who present with shock or other high-risk features, those with high bleeding risk with fibrinolytic therapy, and those who present >3 to 4 hours after symptom onset and who have short transfer times. Patients best suited for initial fibrinolytic therapy are those with low bleeding risk who present very early after symptom onset (<2 to 3 hours) to a non–PCI-capable hospital and who have longer delay to PCI.

Because patients with STEMI may first present with cardiac arrest, regional systems also should emphasize early access to care (recognition of the problem and bystander activation of EMS), rapid dispatch, bystander cardiopulmonary resuscitation (CPR), defibrillation when indicated, advanced cardiac life support, and an organized approach to postresuscitation care. In addition, family members of patients who have had STEMI or other manifestations of coronary artery disease should be referred to CPR training programs that have a social support component and can familiarize them with the use of automated external defibrillators.

Checklist. Improving Door-to-Device Times

1. Prehospital ECG to diagnose STEMI is used to activate the PCI team while the patient is en route to the hospital.
2. Emergency physicians activate the PCI team.
3. A single call to a central page operator activates the PCI team.
4. Goal is set for the PCI team to arrive in the catheterization laboratory with in 20 minutes after being paged.
5. Timely data feedback and analysis are provided to members of the STEMI care team.

3.4.1.2. Strategies for Shortening Door-to-Device Times

The D2B time interval includes 3 key components: door-to-ECG time, ECG–to–catheterization laboratory time, and laboratory arrival–to–device time.[132] All 3 intervals are dependent on system factors that may vary across institutions.[132]

Public reporting and national initiatives have focused much attention on D2B times[104,133] and the many reasons for system delays.[134] Studies have shown marked differences in the timeliness of primary PCI across hospitals. Focusing on the processes of care at the top-performing institutions, research has revealed characteristics of institutions associated with exemplary performance.[124] Top hospitals have specific cultural attributes that include 1) a commitment to an explicit goal of improving D2B times that is motivated by internal and external pressures, including senior management support; 2) innovative protocols; 3) flexibility in refining standardized protocols; 4) uncompromising individual clinical leaders; 5) collaborative teams; 6) data feedback to monitor progress, identify problems, and successes; and 7) an organizational culture that fosters resilience to challenges or setbacks to improvement efforts.[135] In addition, several key processes are associated strongly with more timely treatment (Checklist). Other studies have indicated that PCI-capable hospitals receiving patients in transfer can reduce their D2B times by coordinating with the referring hospitals and activating their systems while patients are being transported.[78]

Currently, it is estimated that almost 90% of patients presenting to a hospital with PCI capability and without a clinical reason for delay have a D2B time ≤90 minutes.[136] Some innovative programs are achieving much faster times.[137–139] In addition, with improvements in timeliness of care across the country, racial disparities in reperfusion times have been reduced significantly.[140] In an analysis of patients with STEMI reported by hospitals to the Centers for Medicare & Medicaid Services, median D2B times fell from 96 minutes in the year ending December 31, 2005, to 64 minutes in the 3 quarters ending September 30, 2010. This decline was accompanied by an increase in the percentage of patients with D2B times <90 minutes, from 44.2% to 91.4%.[141] Nevertheless, despite substantial improvements in D2B times, evidence that these efforts have translated into reduced mortality rates is lacking. The absence of demonstrated benefit may relate to reduced power to show change in

survival in a population with a relatively low mortality rate, improved early survival of higher-risk patients, and changing STEMI demographics. These findings support the goal of comprehensive efforts to improve all aspects of acute MI care to improve survival rates.

3.5. Prehospital Fibrinolytic Therapy

The time delay from symptom onset to treatment can be shortened by administration of prehospital fibrinolytic therapy by a trained EMS unit either with a physician on board[142–147] or with a hospital-based physician[148–152] in direct contact, especially in rural areas. Multiple randomized controlled trials (RCTs) have demonstrated the safety and feasibility of prehospital fibrinolytic therapy, with decreased treatment times ranging from 30 to 140 minutes.[42,143,145–147,149–151,153] A meta-analysis of 6 higher-quality RCTs revealed an approximately 60-minute reduction in time from symptom onset to delivery of fibrinolytic therapy with prehospital versus hospital-based administration, with a corresponding 17% reduction in risk of all-cause hospital mortality.[154] Analysis of a subgroup of patients enrolled in the CAPTIM (Comparaison de l'Angioplastie Primaire et de la Thrombolyse) trial within 2 hours of symptom onset showed a significantly lower 5-year mortality rate for patients treated with prehospital fibrinolysis than for patients managed with primary PCI (P=0.04).[123,142] These salutary results for early presenters were confirmed in a subsequent analysis of combined data from the CAPTIM and WEST (Which Early ST-Elevation Myocardial Infarction Therapy) trials.[155] Data from the USIC (Unité de Soins Intensifs Coronaires) Registry and the Swedish Registry of Cardiac Intensive Care also suggest that prehospital fibrinolytic therapy may lower STEMI mortality rates.[144,148]

At the present time, however, prehospital fibrinolytic therapy is not used in most communities in the United States. EMS in rural areas, where prehospital fibrinolysis would potentially be of benefit, often have neither the resources to train paramedics nor the funding for necessary equipment. Use of prehospital fibrinolysis is more widespread in some regions of Europe and the United Kingdom. The writing committee endorses the need for further research into the implementation of prehospital strategies to reduce total ischemic time.

3.6. The Relationship Between Sudden Cardiac Death and STEMI

3.6.1. Evaluation and Management of Patients With STEMI and Out-of-Hospital Cardiac Arrest: Recommendations

Class I

1. **Therapeutic hypothermia should be started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest caused by ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), including patients who undergo primary PCI.[156–158] (*Level of Evidence: B*)**
2. **Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI.[159–174] (*Level of Evidence: B*)**

See *Online Data Supplement 2* for additional data on PCI for cardiac arrest.

Almost 70% of the coronary heart disease deaths annually in the United States occur out of hospital, usually presenting as "sudden death" due to cardiac arrest.[175] Resuscitation is attempted by EMS personnel in approximately 60% of these out-of-hospital cardiac arrest cases; the remaining patients are deceased on arrival of the EMS team.[175–177] Although only 23% of out-of-hospital cardiac arrest cases have a shockable initial rhythm (primarily VF), the majority of neurologically intact survivors come from this subgroup.[175,176] The median rate of survival to hospital discharge with any first recorded rhythm is only 7.9%[175]; the rate of survival in patients who are in VF initially is much higher (median 22%, range 8% to 40%), as documented in 10 US and Canadian regions participating in the National Institutes of Health–sponsored Resuscitation Outcomes Consortium.[176]

Survival from out-of-hospital cardiac arrest is optimal when both CPR and defibrillation are initiated early.[178] Survival from VF specifically is inversely related to the time interval between its onset and termination, with the odds of survival decreasing 7% to 10% for each minute of delay from onset to defibrillation.[178–180] The percentage of patients who are found in VF and the likelihood of survival are higher if the patient's collapse is witnessed, if bystander CPR is performed, and if a monitor/defibrillator can be applied quickly.[181]

Community strategies that improve the delivery of early defibrillation to out-of-hospital cardiac arrest victims include training and equipping first responders (fire and law enforcement), EMS personnel, and paramedics to defibrillate, as well as placing automated external defibrillators in highly populated locations such as airports, commercial aircraft, and gambling casinos ("public access defibrillation").[182–193] The latter strategy has been shown to approximately double the number of neurologically intact out-of-hospital cardiac arrest survivors when laypersons are trained and equipped to provide early CPR and defibrillation with automated external defibrillators, compared with providing CPR alone while awaiting arrival of EMS personnel.[183]

Two RCTs have reported improved rates of neurologically intact survival to hospital discharge when comatose patients with out-of-hospital VF or nonperfusing VT cardiac arrest were cooled to 32°C to 34°C for 12 or 24 hours beginning minutes to hours after the return of spontaneous circulation.[157,158] Additional studies with historical control groups also have shown improved neurological outcomes after therapeutic hypothermia for comatose survivors of VF arrest.[194,195] Accordingly, therapeutic hypothermia should be initiated in patients with STEMI and out-of-hospital cardiac arrest. Cooling should begin before or at the time of cardiac catheterization.

Approximately 5% of patients with STEMI who survive to reach the hospital will experience a cardiac arrest during hospitalization.[196] Reports from high-volume PCI centers indicate that 4% to 11% of patients with STEMI who are

treated with PCI are brought to cardiac catheterization after being resuscitated from out-of-hospital cardiac arrest.[77,197,198] However, the percentage of out-of-hospital cardiac arrest victims whose event is triggered by an acute coronary occlusion is less clear. The majority of out-of-hospital cardiac arrest patients who cannot be resuscitated have significant coronary atherosclerosis.[199] Coronary atherosclerosis is also present in the majority of cardiac arrest victims who survive and undergo coronary angiography.[200] Because of the high prevalence of acute coronary artery occlusions in out-of-hospital cardiac arrest patients who are resuscitated successfully, especially those whose initial rhythm is VF in the setting of STEMI, the AHA 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care[201] recommend emergency coronary angiography with prompt opening of the infarct artery. Out-of-hospital cardiac arrest victims with initial VF who survive to hospital admission have a rate of survival to hospital discharge of 60% after early PCI.

The AHA issued a policy statement calling for communities to establish regional systems of care for out-of-hospital cardiac arrest.[159] The statement defines 2 different levels of cardiac resuscitation centers and lists the essential elements of such a system. PCI-capable hospitals become ideal candidates to serve as Level I cardiac resuscitation centers that can offer a wide range of services, including timely PCI when indicated, a goal-directed care bundle,[202,203] therapeutic hypothermia,[157,158] frequent or continuous electroencephalographic monitoring, a multidisciplinary team approach, and neuropsychiatric evaluation for survivors. All other participating hospitals should be trained and equipped as Level II cardiac resuscitation centers, which are capable of initiating therapeutic hypothermia and transferring patients for primary postresuscitation care. Ideally, out-of-hospital cardiac arrest outcomes should be measured and compared within a dedicated registry. Lastly, it is important for organizations that collect and publicly report STEMI and PCI data to consider resuscitated out-of-hospital cardiac arrest patients separately from their hospital and individual operator quality "scorecards" because such patients, even with optimal care, have a much higher mortality rate than that of patients with STEMI who have not had a cardiac arrest.[204–206] Public reporting in this instance might have the unintended consequence of reducing appropriate care.[207]

4. Reperfusion at a PCI-Capable Hospital

4.1. Primary PCI

4.1.1. Primary PCI in STEMI: Recommendations

See Table 2 for a summary of recommendations from this section.

Class I

1. **Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration.[82,208,209] (*Level of Evidence: A*)**
2. **Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC.[210,211] (*Level of Evidence: B*)**
3. **Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset (Section 9.1.1).[212–215] (*Level of Evidence: B*)**

Class IIa

1. **Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset.[94,95] (*Level of Evidence: B*)**

Class III: Harm

1. **PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable.[216–218] (*Level of Evidence: B*)**

Table 2. Primary PCI in STEMI

	COR	LOE	References
Ischemic symptoms <12 h	I	A	82, 208, 209
Ischemic symptoms <12 h and contraindications to fibrinolytic therapy irrespective of time delay from FMC	I	B	210, 211
Cardiogenic shock or acute severe HF irrespective of time delay from MI onset	I	B	212–215
Evidence of ongoing ischemia 12 to 24 h after symptom onset	IIa	B	94, 95
PCI of a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B	216–218

COR indicates Class of Recommendation; FMC, first medical contact; HF, heart failure; LOE, Level of Evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Primary PCI of the infarct artery is preferred to fibrinolytic therapy when time-to-treatment delays are short and the patient presents to a high-volume, well-equipped center with experienced interventional cardiologists and skilled support staff. Compared with fibrinolytic therapy, primary PCI produces higher rates of infarct artery patency, TIMI 3 flow, and access site bleeding and lower rates of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage (ICH), and death.[82] Early, successful PCI also greatly decreases the complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, allowing earlier hospital discharge and resumption of daily activities. Primary PCI has its greatest survival benefit in high-risk patients. PCI outcomes have been shown to be worse with delays to treatment and with low-volume hospitals and operators. Quality metrics for both laboratory and operator performance and considerations with regard to primary PCI at hospitals without on-site cardiac surgery are reviewed in the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, Section 7.[219]

Potential complications of primary PCI include problems with the arterial access site; adverse reactions to volume loading, contrast medium, and antithrombotic medications; technical complications; and reperfusion events. The "no-reflow" phenomenon refers to suboptimal myocardial perfusion despite restoration of epicardial flow in the infarct artery and has been attributed to the combined effects of inflammation, endothelial injury, edema, atheroembolization, vasospasm, and myocyte reperfusion injury.[220] No-reflow is associated with a reduced survival rate. Treatment and prevention strategies have included use of the GP IIb/IIIa antagonist abciximab, vasodilators (nitroprusside, verapamil, adenosine), and inhibitors of various metabolic pathways (nicorandil, pexelizumab), albeit without consistent effect. Manual thrombus aspiration at the time of primary PCI results in improved tissue perfusion and more complete ST resolution[221,222] (Section 4.2), though not all studies have shown positive results.[223]

PCI of a noninfarct artery with TIMI 3 flow at the time of primary PCI in hemodynamically stable patients has been associated with worse clinical outcomes in several studies,[216–218,224] though others have suggested that it may be performed safely.[225–229] Noninfarct artery PCI is not recommended in this context unless multiple complex lesions are seen on angiography and ECG localization of the infarct is ambiguous.[230,231] Clinical stability may be defined broadly as the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia. In patients with cardiogenic shock due to pump failure, PCI of a severe stenosis in a large noninfarct artery might improve hemodynamic stability and should be considered during the primary procedure (Section 9.1.1). In the majority of patients, delayed PCI can be performed in a noninfarct artery at a later time if indicated by clinical events or the results of noninvasive testing.[218,232,233]

4.2. Aspiration Thrombectomy: Recommendation

Class IIa

1. **Manual aspiration thrombectomy is reasonable for patients undergoing primary PCI.[221,223,234,235] (*Level of Evidence: B*)**

Two RCTs[221,235] and a meta-analysis[234] support the use of manual aspiration thrombectomy during primary PCI to improve microvascular reperfusion and to decrease deaths and adverse cardiac events. However, infarct size was not reduced by manual aspiration thrombectomy in the INFUSE-AMI (Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) trial of patients with large anterior STEMI.[223] The trial was underpowered to detect differences in clinical outcomes. No clinical benefit for routine rheolytic thrombectomy has been demonstrated in primary PCI.[234,236,237]

4.3. Use of Stents in Primary PCI

4.3.1. Use of Stents in Patients With STEMI: Recommendations

Class I

1. **Placement of a stent (bare-metal stent [BMS] or drug-eluting stent [DES]) is useful in primary PCI for patients with STEMI.[238,239] (*Level of Evidence: A*)**
2. **BMS† should be used in patients with high bleeding risk, inability to comply with 1 year of dual antiplatelet therapy (DAPT), or anticipated invasive or surgical procedures in the next 1 year. (*Level of Evidence: C*)**

Class III: Harm

1. **DES should not be used in primary PCI for patients with STEMI who are unable to tolerate or comply with a prolonged course of DAPT because of the increased risk of stent thrombosis with premature discontinuation of one or both agents.[240–246] (*Level of Evidence: B*)**

Coronary stents are used routinely at the time of primary PCI. Compared with balloon angioplasty, BMS implantation during primary PCI decreases the risk for subsequent target-lesion and target-vessel revascularization and possibly the risk for reinfarction, but is not associated with a reduction in the mortality rate.[238] Compared with BMS, DES implantation decreases restenosis rates and the need for reintervention but does not definitively reduce rates of death or reinfarction. Notably, DES in this setting does not increase the risk of early or late stent thrombosis.[242–245,247,248] Controversy remains as to whether the risk of very late stent thrombosis is higher with first-generation DES than with BMS.[249] The lowest rates of stent thrombosis have been reported with cobalt-chromium everolimus-eluting stents.[250] The greatest challenge in deciding the approach at the time of primary PCI, however, is determining emergently whether the patient is a candidate for a prolonged (ie, 1 year) course of DAPT. DES should be avoided in the presence of financial or social barriers that may limit patient compliance, elevated bleeding risk, the anticipated need for invasive or surgical procedures in the subsequent 1 year, or an independent indication for long-term anticoagulant therapy.

4.4. Adjunctive Antithrombotic Therapy for Primary PCI

See Table 3 for a summary of recommendations from this section and *Online Data Supplement 3* for additional information on antithrombotic therapy.

4.4.1. Antiplatelet Therapy to Support Primary PCI for STEMI: Recommendations

Class I

1. **Aspirin 162 to 325 mg should be given before primary PCI.[251–253] (*Level of Evidence: B*)**

†Balloon angioplasty without stent placement may be used in selected patients.

Table 3. Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg load before procedure	I	B	251–253
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A	254, 255, 257
• 81 mg daily is the preferred maintenance dose*	IIa	B	253, 254, 263, 264
$P2Y_{12}$ inhibitors			
Loading doses			
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B	253, 258, 259
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B	260
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B	261
Maintenance doses and duration of therapy			
DES placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	260, 262
• Prasugrel: 10 mg daily	I	B	262
• Ticagrelor: 90 mg twice a day*	I	B	261
BMS† placed: Continue therapy for 1 y with:			
• Clopidogrel: 75 mg daily	I	B	260, 262
• Prasugrel: 10 mg daily	I	B	262
• Ticagrelor: 90 mg twice a day*	I	B	261
DES placed:			
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 y	IIb	C	N/A
• Patients with STEMI with prior stroke or TIA: prasugrel	III: Harm	B	260
IV GP IIb/IIIa receptor antagonists in conjunction with UFH or bivalirudin in selected patients			
• Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min)	IIa	A	265–267
• Tirofiban: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min	IIa	B	268, 269
◦ In patients with CrCl <30 mL/min, reduce infusion by 50%			
• Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus	IIa	B	270
◦ In patients with CrCl <50 mL/min, reduce infusion by 50%			
◦ Avoid in patients on hemodialysis			
• Pre–catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B	103, 268, 271–277
• Intracoronary abciximab 0.25-mg/kg bolus	IIb	B	223, 278–284
Anticoagulant therapy			
• UFH:	I	C	N/A
◦ With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡			
◦ With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT§	I	C	N/A
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg can be given if needed.	I	B	248
◦ Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min			
◦ Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa	B	248
• Fondaparinux: Not recommended as sole anticoagulant for primary PCI	III: Harm	B	304

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

†Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone according to the recommendations listed for BMS. (*LOE: C*)

‡The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 s.

§The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 s (HemoTec device) or 300 to 350 s (Hemochron device).

ACT indicates activated clotting time; BMS, bare-metal stent; CrCl, creatinine clearance; COR, Class of Recommendation; DES, drug-eluting stent; GP, glycoprotein; IV, intravenous; LOE, Level of Evidence; N/A, not available; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; and UFH, unfractionated heparin.

2. **After PCI, aspirin should be continued indefinitely.[254,255,257] (*Level of Evidence: A*)**
3. **A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include**
   a. **Clopidogrel 600 mg[253,258,259] (*Level of Evidence: B*); or**
   b. **Prasugrel 60 mg[260] (*Level of Evidence: B*); or**
   c. **Ticagrelor 180 mg.[261] (*Level of Evidence: B*)**
4. **$P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:**
   a. **Clopidogrel 75 mg daily[260,262] (*Level of Evidence: B*); or**
   b. **Prasugrel 10 mg daily[262] (*Level of Evidence: B*); or**
   c. **Ticagrelor 90 mg twice a day.[261]‡ (*Level of Evidence: B*)**

Class IIa

1. **It is reasonable to use 81 mg of aspirin in preference to higher maintenance doses after primary PCI.[253,254,263,264] (*Level of Evidence: B*)**
2. **It is reasonable to begin treatment with an intravenous GP IIb/IIIa receptor antagonist such as abciximab[265–267] (*Level of Evidence: A*), high-bolus-dose tirofiban[268,269] (*Level of Evidence: B*), or double-bolus eptifibatide[270] (*Level of Evidence: B*) at the time of primary PCI (with or without stenting or clopidogrel pretreatment) in selected patients with STEMI who are receiving unfractionated heparin (UFH).**

Class IIb

1. **It may be reasonable to administer intravenous GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (eg, ambulance, ED) to patients with STEMI for whom primary PCI is intended.[103,268,271–277] (*Level of Evidence: B*)**
2. **It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI.[223,278–284] (*Level of Evidence: B*)**
3. **Continuation of a $P2Y_{12}$ inhibitor beyond 1 year may be considered in patients undergoing DES placement. (*Level of Evidence: C*)**

Class III: Harm

1. **Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.[260] (*Level of Evidence: B*)**

Although the minimum effective aspirin dose in the setting of PCI for STEMI has not been established prospectively, the writing committee recommends that an empiric dose of 325 mg be given as early as possible before PCI and a maintenance dose continued indefinitely thereafter. It is the consensus of the writing committee that the 81-mg maintenance dose is preferred even among patients who receive a stent during primary PCI. This recommendation is based on evidence of an increased risk of bleeding in most studies comparing higher- with lower-dose aspirin,[253,254,263,264] as well as the absence of data from RCTs demonstrating superior efficacy of higher aspirin doses in this setting. However, because the CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes) trial did not report differences in either efficacy or safety in patients with STEMI randomized to 81 mg versus 325 mg of aspirin, the committee did not think that the evidence favoring 81 mg over higher dosages was sufficiently conclusive to merit a Class I recommendation.[253]

Loading doses of $P2Y_{12}$ inhibitors are provided before or at the time of primary PCI. These agents are continued in a maintenance dose for 1 year after PCI with a stent (BMS or DES) in the absence of bleeding. A 600-mg loading dose of clopidogrel is preferred to a 300-mg loading dose, given the more extensive and rapid platelet inhibition achieved with the higher dose, as well as the beneficial effects reported in a CURRENT-OASIS 7 subgroup analysis.[259] The underpowered ARMYDA-6 MI (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty–Myocardial Infarction) study also reported beneficial surrogate outcomes with the higher clopidogrel loading dose.[258]

The antiplatelet response to clopidogrel may vary as a function of patient phenotype (obesity, diabetes mellitus), enteric *ABCB 1* polymorphisms, hepatic *CYP450* enzyme system polymorphisms (predominantly *CYP 2C19*2*), and medications that interfere with clopidogrel biotransformation. Approximately 25% to 30% of patients may harbor a reduced-function *CYP2C19* allele. In TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis In Myocardial Infarction)[285] and 3 cohort studies,[286–288] patients who were carriers of the reduced-function *CYP2C19*2* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and increased rates of major adverse cardiovascular events and stent thrombosis.[285] The US Food and Drug Administration has changed clopidogrel's prescribing information to highlight the potential impact of *CYP2C19* genotype on clopidogrel pharmacokinetics and clinical response.[289] Nevertheless, other studies have not confirmed associations between *CYP2C19* polymorphisms and adverse outcomes in clopidogrel-treated patients.[290] Future studies are needed to further clarify the risk associated with these genetic polymorphisms and to develop effective therapeutic strategies for carriers of allelic variants of responsible enzyme systems. Proton-pump inhibitors, most prominently omeprazole, can interfere with clopidogrel metabolism and result in diminished in vitro antiplatelet effect,[291] but it does not appear that this pharmacokinetic effect translates into worse clinical outcomes.[291,292]

Prasugrel, an alternative thienopyridine, achieves greater inhibition of platelet aggregation than clopidogrel. In the TRITON-TIMI 38 trial[260] of prasugrel versus clopidogrel in patients with ACS for whom an invasive strategy was planned, patients with STEMI who were assigned to prasugrel had a lower 30-day rate of the composite primary outcome. This difference persisted to 15 months. In addition, the rate of stent thrombosis

‡The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

reported at 30 days was significantly lower with prasugrel.[260,262] The loading dose of clopidogrel in TRITON-TIMI 38, which rarely was administered before coronary angiography and was limited to 300 mg, may have contributed to differences in efficacy and safety between treatment groups.[262]

The benefits of prasugrel relative to clopidogrel in STEMI must be weighed against the increase in the risk of bleeding associated with its use. Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack and was not shown to be beneficial in patients ≥75 years of age or patients who weigh <60 kg.[260] In TRITON-TIMI 38, interaction testing for efficacy and safety showed no significant difference in bleeding risk across the spectrum of ACS. Prasugrel may be best suited for younger patients with diabetes mellitus or large areas of myocardium at risk, who are also at low bleeding risk, have the ability to continue a regimen of DAPT, and have no anticipation of surgery over the subsequent 1 year. The package insert for prasugrel suggests that a lower maintenance dose of 5 mg daily might be considered for patients at high risk of bleeding, though this dose has not been prospectively studied.[293]

Ticagrelor is a reversible, nonthienopyridine $P2Y_{12}$ receptor antagonist that does not require metabolic conversion to active drug. The PLATO (Platelet Inhibition and Patient Outcomes) study compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) with clopidogrel (300- or 600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18 624 patients with ACS, of whom 35% had STEMI.[294] Among the 7544 patients enrolled with ST elevation or LBBB who underwent primary PCI, findings were consistent with the overall trial results. Significant reductions favoring ticagrelor were seen in the primary PCI subgroup for stent thrombosis and total deaths, though there were more strokes and episodes of ICH with ticagrelor.[261] A prespecified subgroup analysis in the PLATO trial showed a significant interaction between treatment effect and geographic region, with an apparently smaller ticagrelor effect in North America than in other areas. Although this interaction could have been due to chance alone,[295] a contribution from higher aspirin doses, as more commonly used in the United States, cannot be excluded. When provided long term with ticagrelor as a component of DAPT, the dose of aspirin should not exceed 100 mg.[293]

Although 1 year of DAPT is recommended after stent implantation during primary PCI for STEMI, earlier discontinuation of a $P2Y_{12}$ inhibitor may be necessary if the risk of morbidity from bleeding outweighs the anticipated benefit of DAPT. Clinical judgment is required, and discussion with the interventional cardiologist is recommended.

DAPT with aspirin and either clopidogrel or prasugrel has increased the risk of ICH in several clinical trials and patient populations (especially in those with prior stroke).[260,296–298] In PLATO, the number of patients with prior stroke was small, limiting the power to detect treatment differences in intracranial bleeding in this subgroup.[299] Until further data become available, it would seem prudent to weigh the possible increased risk of intracranial bleeding when the addition of ticagrelor to aspirin is considered in patients with prior stroke or transient ischemic attack.[300]

Evidence to support the use of intravenous GP IIb/IIIa receptor antagonists in patients with STEMI was established largely before the use of oral DAPT. Although several studies have failed to show benefit with the administration of "upstream" GP IIb/IIIa receptor antagonists before primary PCI in the setting of DAPT with either UFH or bivalirudin anticoagulation,[103,268,271–27] a meta-analysis restricted to the use of abciximab has suggested it may be useful in this setting.[277] The adjunctive use of GP IIb/IIIa agents at the time of PCI can be considered on an individual basis for large thrombus burden or inadequate $P2Y_{12}$ receptor antagonist loading.[265–270,301] For patients receiving bivalirudin as the primary anticoagulant, routine adjunctive use of GP IIb/IIIa inhibitors is not recommended[248] but may be considered as adjunctive or "bail-out" therapy in selected cases.[223,301–303] Studies of intracoronary GP IIb/IIIa administration during primary PCI have shown mixed results for a variety of surrogate and combined clinical endpoints. Use of intracoronary abciximab may be reasonable in select cases.[223,278–284]

4.4.2. Anticoagulant Therapy to Support Primary PCI: Recommendations

Class I

1. **For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended:**
   a. **UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered (*Level of Evidence: C);* or**
   b. **Bivalirudin with or without prior treatment with UFH.[248] (*Level of Evidence: B*)**

Class IIa

1. **In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist.[248] (*Level of Evidence: B*)**

Class III: Harm

1. **Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis.[304] (*Level of Evidence: B*)**

Intravenous UFH titrated to an appropriate activated clotting time is a familiar and well-tested strategy for anticoagulant therapy at the time of PCI for STEMI. Enoxaparin and fondaparinux have been studied less extensively in this setting. The ATOLL (Acute STEMI Treated with Primary PCI and IV Enoxaparin or UFH to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up) trial comparing intravenous enoxaparin with UFH for primary PCI failed to meet its primary, composite endpoint.[305] Fondaparinux has been associated with catheter thrombosis in this setting.[304] On the basis of the findings in the HORIZONS-

Table 4. Indications for Fibrinolytic Therapy When There Is a >120-Minute Delay From FMC to Primary PCI (Figure 2)

	COR	LOE	References
Ischemic symptoms <12 h	I	A	81, 306–311
Evidence of ongoing ischemia 12 to 24 h after symptom onset, and a large area of myocardium at risk or hemodynamic instability	IIa	C	N/A
ST depression except if true posterior (inferobasal) MI suspected or when associated with ST-elevation in lead aVR	III: Harm	B	10, 11, 81, 312, 313

COR indicates Class of Recommendation; FMC, first medical contact; LOE, Level of Evidence; MI, myocardial infarction; N/A, not available; and PCI, percutaneous coronary intervention.

AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial,[248] the writing committee considers bivalirudin, in combination with oral DAPT, a reasonable anticoagulant alternative for primary PCI in STEMI, regardless of whether pretreatment was given with UFH, especially for patients at higher risk of bleeding and when avoidance of GP IIb/IIIa antagonists is desired. Bivalirudin in this setting may provide a long-term survival benefit related to decreased bleeding but with a higher risk of early stent thrombosis.[248]

5. Reperfusion at a Non–PCI-Capable Hospital

5.1. Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC: Recommendations

See Table 4 for a summary of recommendations from this section.

Class I

1. **In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC.[81,306–311] (*Level of Evidence: A*)**

Class IIa

1. **In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. (*Level of Evidence: C*)**

Class III: Harm

1. **Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR.[10,11,81,312,313] (*Level of Evidence: B*)**

5.1.1. Timing of Fibrinolytic Therapy

The benefits of fibrinolytic therapy in patients with ST elevation or bundle-branch block MI are well established, with a time-dependent reduction in both mortality and morbidity rates during the initial 12 hours after symptom onset.[81,306–311,314–320] As noted in Section 3.2, even when interhospital transport times are short, there may be advantages to the immediate delivery of fibrinolytic therapy versus any delay to primary PCI for patients with STEMI and low bleeding risk who present within the first 1 to 2 hours of symptom onset.[123,321] Benefit from fibrinolytic therapy in patients who present >12 hours after symptom onset has not been established,[81,307,309,322,323] although there remains consensus that consideration should be given to administering a fibrinolytic agent in symptomatic patients presenting >12 hours after symptom onset with STEMI and a large area of myocardium at risk or hemodynamic instability if PCI is unavailable.[4,48]

5.1.2. Choice of Fibrinolytic Agent

Table 5 lists currently available fibrinolytic agents.[314,324–326,328,329] Fibrin-specific agents are preferred when available. Adjunctive antiplatelet and/or anticoagulant therapies are indicated, regardless of the choice of fibrinolytic agent.

Table 5. Fibrinolytic Agents

Fibrinolytic Agent	Dose	Fibrin Specificity*	Antigenic	Patency Rate (90-min TIMI 2 or 3 flow)
Fibrin-specific:				
Tenecteplase (TNK-tPA)	Single IV weight-based bolus†	++++	No	85%[328]
Reteplase (rPA)	10 U + 10-U IV boluses given 30 min apart	++	No	84%[314]
Alteplase (tPA)	90-min weight-based infusion‡	++	No	73% to 84%[314, 324, 326]
Non–fibrin-specific:				
Streptokinase§	1.5 million units IV given over 30–60 min	No	Yes‖	60% to 68%[324, 329]

*Strength of fibrin specificity; "++++" is more strong, "++" is less strong.

†30 mg for weight <60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; and 50 mg for ≥90 kg.

‡Bolus 15 mg, infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg.

§Streptokinase is no longer marketed in the United States but is available in other countries.

‖Streptokinase is highly antigenic and absolutely contraindicated within 6 mo of previous exposure because of the potential for serious allergic reaction.

IV indicates intravenous; rPA, reteplase plasminogen activator; TIMI, Thrombolysis In Myocardial Infarction; TNK-tPA, tenecteplase tissue-type plasminogen activator; and tPA, tissue-type plasminogen activator.

Table 6. Contraindications and Cautions for Fibrinolytic Therapy in STEMI*

Absolute contraindications

- Any prior ICH
- Known structural cerebral vascular lesion (eg, arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 mo
  - EXCEPT acute ischemic stroke within 4.5 h
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed-head or facial trauma within 3 mo
- Intracranial or intraspinal surgery within 2 mo
- Severe uncontrolled hypertension (unresponsive to emergency therapy)
- For streptokinase, prior treatment within the previous 6 mo

Relative contraindications

- History of chronic, severe, poorly controlled hypertension
- Significant hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
- History of prior ischemic stroke >3 mo
- Dementia
- Known intracranial pathology not covered in absolute contraindications
- Traumatic or prolonged (>10 min) CPR
- Major surgery (<3 wk)
- Recent (within 2 to 4 wk) internal bleeding
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer
- Oral anticoagulant therapy

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

CPR indicates cardiopulmonary resuscitation; DBP; diastolic blood pressure; ICH, intracranial hemorrhage; SBP, systolic blood pressure; and STEMI, ST-elevation myocardial infarction.

5.1.3. Contraindications and Complications With Fibrinolytic Therapy

Absolute and relative contraindications to fibrinolytic therapy are listed in Table 6. The decision to use fibrinolytic therapy for patients with STEMI is predicated on a risk–benefit analysis that integrates time from onset of symptoms, the clinical and hemodynamic features at presentation, patient comorbidities, risk of bleeding, presence of contraindications, and time delay to PCI (Section 3.2).

5.1.4. Adjunctive Antithrombotic Therapy With Fibrinolysis

See Table 7 for a summary of recommendations from this section.

5.1.4.1. Adjunctive Antiplatelet Therapy With Fibrinolysis: Recommendations

Class I

1. **Aspirin (162- to 325-mg loading dose) and clopidogrel (300-mg loading dose for patients ≤75 years of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy.[308,330,331] (*Level of Evidence: A*)**
2. **Aspirin should be continued indefinitely[308,330,331] (*Level of Evidence: A*) and clopidogrel (75 mg daily) should be continued for at least 14 days[330,331] (*Level of Evidence: A*) and up to 1 year (*Level of Evidence: C*) in patients with STEMI who receive fibrinolytic therapy.**

Class IIa

1. **It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy.[254,257,263,264] (*Level of Evidence: B*)**

The beneficial effects of aspirin and clopidogrel with fibrinolytic therapy are well established.[254,257,263,264] These agents should be given before or with the fibrinolytic.[330] The recommendation that clopidogrel be continued for up to 1 year is extrapolated from the experience with DAPT in patients with non–ST-elevation ACS.[330] The coadministration of other $P2Y_{12}$ antagonists with fibrinolytic therapy has not been prospectively studied.

5.1.4.2. Adjunctive Anticoagulant Therapy With Fibrinolysis: Recommendations

Class I

1. **Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the index hospitalization, up to 8 days or until revascularization if performed.[318,332] (*Level of Evidence: A*) Recommended regimens include**
   a. **UFH administered as a weight-adjusted intravenous bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization. (*Level of Evidence: C);***
   b. **Enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization.[332–335] (*Level of Evidence: A*); or**
   c. **Fondaparinux administered with initial intravenous dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to 8 days or until revascularization.[304] (*Level of Evidence: B*)**

Anticoagulation is recommended in support of fibrin-specific therapy to improve vessel patency and prevent reocclusion.[336] Dosing of UFH is predicated on the activated partial thromboplastin time, and monitoring of platelet counts to avoid the risks of excess bleeding and heparin-induced thrombocytopenia (HIT) is advised.[318,337–339] UFH may be given as an intravenous bolus and infusion for patients receiving streptokinase if they are at high risk for systemic embolization. Enoxaparin is preferred over UFH for anticoagulation extending beyond 48 hours. Caution is advised when enoxaparin is administered to patients

Table 7. Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg loading dose	I	A	308, 330, 331
• 81- to 325-mg daily maintenance dose (indefinite)	I	A	308, 330, 331
• 81 mg daily is the preferred maintenance dose	IIa	B	254, 257, 263, 264
$P2Y_{12}$ receptor inhibitors			
• Clopidogrel:	I	A	330, 331
• Age ≤75 y: 300-mg loading dose			
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)	330, 331
		C (up to 1 y)	N/A
• Age >75 y: no loading dose, give 75 mg	I	A	330, 331
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)	330, 331
		C (up to 1 y)	N/A
Anticoagulant therapy			
• UFH:	I	C	N/A
• Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization.			
• Enoxaparin:	I	A	332–335
• If age <75 y: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses)			
• If age ≥75 y: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first 2 doses)			
• Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h			
• Duration: For the index hospitalization, up to 8 d or until revascularization			
• Fondaparinux:	I	B	304
• Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization			
• Contraindicated if CrCl <30 mL/min			

aPTT indicates activated partial thromboplastin time; COR, Class of Recommendation; CrCl, creatinine clearance; IV, intravenous; LOE, Level of Evidence; N/A, not available; and UFH, unfractionated heparin.

with impaired renal function.[340] Fondaparinux should not be given as the sole anticoagulant to patients referred for PCI and is contraindicated for patients with a creatinine clearance <30 mL/min.[304,341] Bivalirudin may be used for patients treated with a fibrinolytic agent who develop HIT and require continued anticoagulation.[342]

5.2. Assessment of Reperfusion After Fibrinolysis

TIMI 3 flow after fibrinolytic therapy predicts subsequent short- and long-term survival.[343–345] Traditional variables that have been used to assess the angiographic response to fibrinolytic therapy are imprecise[346] and have included an improvement in or relief of chest pain, resolution of ST elevation, and the presence of reperfusion arrhythmias (eg, accelerated idioventricular rhythm). The relatively sudden and complete relief of chest pain coupled with >70% ST resolution (in the index lead showing the greatest degree of elevation on presentation) is highly suggestive of restoration of normal myocardial blood flow. Complete (or near complete) ST-segment resolution at 60 or 90 minutes after fibrinolytic therapy is a useful marker of a patent infarct artery.[347–351] Conversely, partial or absent improvement in the extent of ST elevation is not as accurate in predicting a "closed artery."[349–351] Lack of improvement in ST resolution is associated with worse prognosis.[349,352,353] The combination of <50% ST resolution and the absence of reperfusion arrhythmias at 2 hours after treatment predicts TIMI flow <3 in the infarct artery with a sensitivity of 81%, specificity 88%, positive predictive value 87%, and negative predictive value 83%.[347] Lack of resolution of ST elevation by at least 50% in the worst lead at 60 to 90 minutes should prompt strong consideration of a decision to proceed with immediate coronary angiography and "rescue" PCI.

5.3. Transfer to a PCI-Capable Hospital After Fibrinolytic Therapy

See Figure 2.

5.3.1. Transfer of Patients With STEMI to a PCI-Capable Hospital for Coronary Angiography After Fibrinolytic Therapy: Recommendations

See Table 8 for a summary of recommendations from this section; *Online Data Supplement 4* for additional data on early catheterization and rescue PCI for fibrinolytic failure in the stent era; and *Online Data Supplement 5* for additional

Table 8. Indications for Transfer for Angiography After Fibrinolytic Therapy

	COR	LOE	References
Immediate transfer for cardiogenic shock or severe acute HF irrespective of time delay from MI onset	I	B	354
Urgent transfer for failed reperfusion or reocclusion	IIa	B	346, 355–357
As part of an invasive strategy in stable* patients with PCI between 3 and 24 h after successful fibrinolysis	IIa	B	358–363

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR indicates Class of Recommendation; HF, heart failure; LOE, Level of Evidence; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

data on early catheterization and PCI after fibrinolysis in the stent era.

Class I

1. **Immediate transfer to a PCI-capable hospital for coronary angiography is recommended for suitable patients with STEMI who develop cardiogenic shock or acute severe HF, irrespective of the time delay from MI onset.[354] (*Level of Evidence: B*)**

Class IIa

1. **Urgent transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who demonstrate evidence of failed reperfusion or reocclusion after fibrinolytic therapy.[346,355–357] (Level of Evidence: B)**
2. **Transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who have received fibrinolytic therapy even when hemodynamically stable§ and with clinical evidence of successful reperfusion. Angiography can be performed as soon as logistically feasible at the receiving hospital, and ideally within 24 hours, but should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.[358–363] (*Level of Evidence: B*)**

5.3.1.1. Transfer for Cardiogenic Shock

The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial[354] demonstrated benefit with coronary angiography and emergency revascularization (with either PCI or CABG) compared with immediate medical stabilization and delayed revascularization in patients with ST-elevation/Q-wave or new LBBB MI and cardiogenic shock (Section 9.1.1). Of note, nearly 50% of patients randomized to the emergency revascularization arm received preprocedural fibrinolytic therapy, and the benefit of emergency revascularization was similar for patients transferred versus those admitted directly to a PCI-capable hospital. For patients with cardiogenic shock, the benefit of emergency revascularization was apparent across a very wide time window, extending up to 54 hours after MI and 18 hours after shock onset.[354] Although PCI should be performed as soon as possible after MI and shock onset, the time window for benefit in this clinical context is more prolonged because of the ongoing "downward ischemic spiral" associated with shock.

5.3.1.2. Transfer for Failure of Fibrinolytic Therapy

Several trials in the stent era and several meta-analyses have examined the role of PCI for fibrinolytic failure[346,355–357,364] (*Online Data Supplement 4*). These studies report a trend toward a lower mortality rate and significantly lower rates of recurrent MI and HF among patients treated with rescue PCI for failed fibrinolysis. For example, in the REACT (Rapid Early Action for Coronary Treatment) study,[355] 427 patients who failed to demonstrate evidence of reperfusion at 90 minutes by ECG criteria were randomized to 1 of 3 treatment arms: rescue PCI, conservative care, or repeat fibrinolytic therapy. The primary endpoint, a composite of death, reinfarction, stroke, or severe HF at 6 months, was significantly lower among patients randomized to rescue PCI than among those randomized to conservative care or repeat fibrinolysis (event-free survival rate: 84.6% versus 70.1% versus 68.7%, P=0.004). The benefit was driven primarily by a reduction in reinfarction; there was no significant survival benefit. Minor bleeding was significantly higher among patients randomized to rescue PCI; however, there were no differences in major bleeding among the 3 groups. Other studies have reported higher rates of periprocedural bleeding and stroke in patients undergoing rescue PCI than in patients treated conservatively.[346,356] The benefit of transferring a patient for PCI of a persistently occluded infarct artery likely would justify these risks if cardiogenic shock, significant hypotension, severe HF, or ECG evidence of an extensive area of myocardial jeopardy (including an anterior infarction or inferior infarction with either right ventricular [RV] involvement or anterior precordial ST depression) is present. In these circumstances, the benefits are greatest if PCI is initiated early after fibrinolytic failure. On the other hand, conservative treatment might be reasonable in a patient with improving symptoms and a limited inferior infarction despite persistence of ST elevation.

5.3.1.3. Transfer for Routine Early Coronary Angiography After Fibrinolytic Therapy

With the introduction of coronary stents and aggressive antiplatelet therapies, there has been renewed interest in immediate and early catheterization after fibrinolytic therapy. The advantage of this approach is that it can be initiated at non–PCI-capable hospitals and affords the healthcare system additional time to arrange a "nonemergency" transfer for angiography and PCI. Routine referral for angiography with the intent to perform PCI is supported indirectly by retrospective analyses from trials of fibrinolytic therapy that suggest that patients treated with PCI during the index hospitalization have a lower risk of recurrent MI and a lower 2-year mortality

§Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

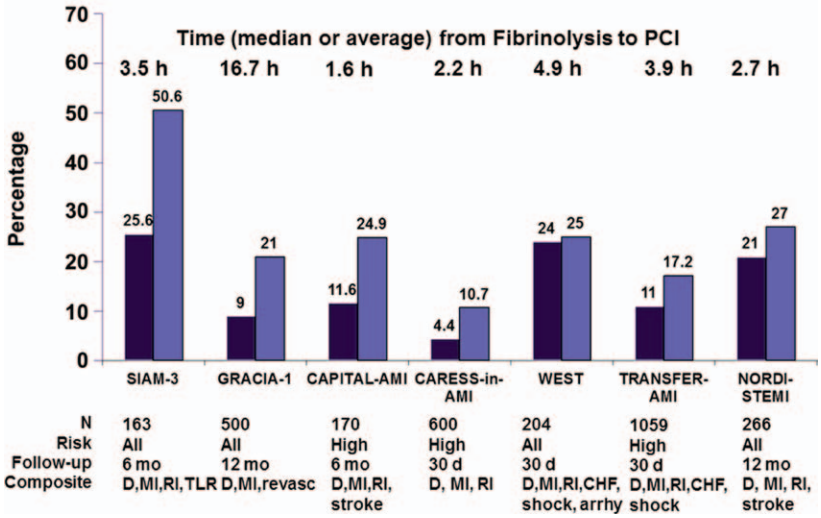

Figure 3. Primary outcome of trials of routine versus ischemia-driven (or delayed) catheterization and PCI after fibrinolytic therapy. The Figure depicts the results of trials comparing routine early catheterization after fibrinolytic therapy with either an ischemia-driven approach or routine delayed catheterization. The y-axis represents the percentage of patients who experienced ≥1 of the clinical trial endpoints. The Figure includes the average (or median) time from fibrinolytic therapy to PCI, the number of patients randomized in each study, the type of patients enrolled in the study (all patients or high-risk patients), the duration of follow-up for the primary endpoint, and the composite primary endpoint for each trial. The darker bars represent patients who underwent routine early catheterization after fibrinolytic therapy. The lighter bars represent patients who underwent either an ischemia-guided or routine delayed catheterization approach. arrhy indicates arrhythmia; CAPITAL-AMI, Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction; CARESS-in-AMI, Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction; CHF, congestive heart failure; D, death; GRACIA, Grup de Analisis de la Cardiopatia Isquemica Aguda; MI, myocardial infarction; NORDISTEMI, Norwegian study on District treatment of ST-Elevation Myocardial Infarction; PCI, percutaneous coronary intervention; revasc, ischemia-driven revascularization; RI, recurrent ischemia; TLR, target-lesion revascularization; TRANSFER-AMI, Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; SIAM-3, Southwest German Interventional Study In Acute Myocardial Infarction; and WEST, Which Early ST-Elevated Myocardial Infarction Therapy.[358,360–362,368–370] Reproduced with permission from Granger.[370a]

rate.[365–367] The results of RCTs evaluating a strategy of routine catheterization after fibrinolysis are limited by small sample sizes or surrogate endpoints and have provided mixed results. Nevertheless, most trials have demonstrated improvement in clinical outcomes in patients transferred for early catheterization, most notably in higher-risk patients[357–362,368–371] (Table 8 and Figure 3). In the GRACIA (Grup de Analisis de la Cardiopatia Isquemica Aguda) study,[362] early catheterization within 6 to 24 hours of successful fibrinolysis in stable patients was compared with an ischemia-guided approach. It resulted in improved outcomes, including a significantly lower rate of death, reinfarction, or ischemia-driven revascularization at 1 year.

The TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study[360] was the largest (n=1059) of the RCTs evaluating transfer for coronary angiography and revascularization among high-risk patients and showed a significant reduction in the combined primary endpoint of death, recurrent MI, recurrent ischemia, new or worsening HF, or shock at 30 days with immediate transfer for the angiography group compared with conservative care. The findings from this and other studies indicate that high-risk patients with STEMI appear to benefit from immediate transfer for early catheterization, compared with either an ischemia-guided approach or delayed routine catheterization at 24 hours to 2 weeks.[360,361] The reported benefits relate to a reduction in the incidence of recurrent infarction or ischemia, thus favoring earlier transfer and revascularization when possible.

The NORDISTEMI (Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction) investigators[358] examined the effect of immediate routine transfer for catheterization versus a conservative strategy with either ischemia-guided treatment in the non–PCI-capable hospital or transfer for rescue PCI. Although this study failed to demonstrate a significant difference between the 2 treatment groups in the incidence of the primary composite endpoint of death, recurrent MI, stroke, or new or recurrent ischemia at 1 year, the incidence of death, recurrent MI, or stroke was significantly lower in the immediate-transfer group. Furthermore, the magnitude of reduction in risk was similar to that reported for high-risk patients in the TRANSFER-AMI study (RR: 0.64; 95% CI: 0.47 to 0.87; P=0.004).[360]

In a meta-analysis[359] that included 7 RCTs of early transfer for catheterization, a strategy of routine early catheterization after fibrinolysis was associated with a statistically significant reduction in the incidence of death or MI at 30 days and at 1 year, without an increase in the risk of major bleeding. This meta-analysis was based on a mixture of trials that randomized high-risk patients[360,361,369] and trials that did not mandate the inclusion of high-risk subjects. A meta-regression analysis investigating the relative benefit of an invasive strategy after fibrinolysis according to the baseline risk of the enrolled patients for each trial suggested a larger proportional benefit with early catheterization and PCI in trials enrolling higher-risk patients.[359]

It is important to recognize that the clinical trials that have addressed routine invasive evaluation after initial pharmaco-

logical management used a time window of 0 to 24 hours for the "early invasive" strategy, thus supporting earlier transfer after administration of fibrinolytic therapy even for patients without high-risk features. However, this time window likely was used in the trial designs to create the greatest possible difference in outcome when compared with the control group (rather than an *a priori* expectation that the benefit would be driven entirely in <24 hours). The writing committee believes that there likely will be continued benefit even beyond 24 hours in those patients with a patent but stenotic infarct artery. In stable patients who are not transferred immediately, catheterization can be considered as part of a routine pharmacoinvasive or ischemia-guided approach >24 hours after administration of fibrinolytic therapy. Because of the associated increased bleeding risk, very early (<2 to 3 hours) catheterization after administration of fibrinolytic therapy with intent to perform revascularization should be reserved for patients with evidence of failed fibrinolysis and significant myocardial jeopardy for whom rescue PCI would be appropriate.

6. Delayed Invasive Management

6.1. Coronary Angiography in Patients Who Initially Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion: Recommendations

See Table 9 for a summary of recommendations from this section.

Class I

1. **Cardiac catheterization and coronary angiography with intent to perform revascularization should be performed after STEMI in patients with any of the following:**
   a. **Cardiogenic shock or acute severe HF that develops after initial presentation[215,354,372,373] (*Level of Evidence: B*);**
   b. **Intermediate- or high-risk findings on predischarge noninvasive ischemia testing[232,233] (*Level of Evidence: B*); or**
   c. **Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (*Level of Evidence: C*)**

Table 9. Indications for Coronary Angiography in Patients Who Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LOE	References
Cardiogenic shock or acute severe HF that develops after initial presentation	I	B	215, 354, 372, 373
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B	232, 233
Spontaneous or easily provoked myocardial ischemia	I	C	N/A
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B	346, 355–357
Stable* patients after successful fibrinolysis, before discharge and ideally between 3 and 24 h	IIa	B	358–363, 374

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR indicates Class of Recommendation; HF, heart failure; LOE, Level of Evidence; and N/A, not available.

Class IIa

1. **Coronary angiography with intent to perform revascularization is reasonable for patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy. Angiography can be performed as soon as logistically feasible.[346,355–357] (*Level of Evidence: B*)**
2. **Coronary angiography is reasonable before hospital discharge in stable§ patients with STEMI after successful fibrinolytic therapy. Angiography can be performed as soon as logistically feasible, and ideally within 24 hours, but should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.[358–363,374] (*Level of Evidence: B*)**

The indications for coronary angiography in patients managed with an initial noninvasive strategy are interwoven with the indications for revascularization (Sections 5.3 and 6.2). Survivors of STEMI with indicators of intermediate or high risk and those with recurrent ischemia or mechanical complications should be considered for coronary angiography and revascularization. In addition, when STEMI is suspected to have occurred by a mechanism other than thrombotic occlusion at the site of an atherosclerotic plaque, coronary angiography may be reasonable to provide diagnostic information and to direct specific therapy. Routine referral for angiography of patients after fibrinolytic therapy is discussed in Section 5.3. Coronary angiography in patients with evidence of failed reperfusion or reocclusion should be performed as soon as logistically feasible.[346,355]

6.2. PCI of an Infarct Artery in Patients Who Initially Were Managed With Fibrinolysis or Who Did Not Receive Reperfusion Therapy: Recommendations

See Table 10 for a summary of recommendations from this section.

Class I

1. **PCI of an anatomically significant stenosis in the infarct artery should be performed in patients with suitable anatomy and any of the following:**
   a. **Cardiogenic shock or acute severe HF[354] (*Level of Evidence: B*);**
   b. **Intermediate- or high-risk findings on predischarge noninvasive ischemia testing[232,233] (*Level of Evidence: C*); or**
   c. **Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (*Level of Evidence: C*)**

§Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

Table 10. Indications for PCI of an Infarct Artery in Patients Who Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LOE	References
Cardiogenic shock or acute severe HF	I	B	354
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	C	232, 233
Spontaneous or easily provoked myocardial ischemia	I	C	N/A
Patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy (as soon as possible)	IIa	B	344–347
Stable* patients after successful fibrinolysis, ideally between 3 and 24 h	IIa	B	358–363
Stable* patients >24 h after successful fibrinolysis	IIb	B	213, 232, 233, 366, 374–378
Delayed PCI of a totally occluded infarct artery >24 h after STEMI in stable patients	III: No Benefit	B	213, 376

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR indicates Class of Recommendation; HF, heart failure; LOE, Level of Evidence; N/A, not available; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Class IIa

1. **Delayed PCI is reasonable in patients with STEMI and evidence of failed reperfusion or reocclusion after fibrinolytic therapy. PCI can be performed as soon as logistically feasible at the receiving hospital.[344–347] (*Level of Evidence: B*)**
2. **Delayed PCI of a significant stenosis in a patent infarct artery is reasonable in stable§ patients with STEMI after fibrinolytic therapy. PCI can be performed as soon as logistically feasible at the receiving hospital, and ideally within 24 hours, but should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.[358–363] (*Level of Evidence: B*)**

Class IIb

1. **Delayed PCI of a significant stenosis in a patent infarct artery greater than 24 hours after STEMI may be considered as part of an invasive strategy in stable§ patients.[213,232,233,366,374–378] (*Level of Evidence: B*)**

Class III: No Benefit

1. **Delayed PCI of a totally occluded infarct artery greater than 24 hours after STEMI should not be performed in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia.[213,376] (*Level of Evidence: B*)**

Delayed PCI of the infarct artery is performed in patients treated with an initial noninvasive strategy (ie, with fibrinolysis or without reperfusion therapy) who become unstable because of the development of cardiogenic shock, acute severe HF, or unstable postinfarction angina, provided that invasive management is not considered futile or inappropriate.[215,379] Delayed PCI also encompasses interventions performed for fibrinolytic failure[355,356] or infarct artery reocclusion, as part of an invasive strategy for patients after successful fibrinolysis,[359–361] and for patients who did not receive reperfusion therapy but who did demonstrate significant residual ischemia during hospitalization. The benefits of routine, ie, non–ischemia-driven, PCI of an angiographically significant stenosis in a patent infarct artery >24 hours after STEMI are less well established.[232,233,378] Delayed PCI of a totally occluded infarct artery >24 hours after STEMI should not be undertaken in clinically stable patients without evidence of severe ischemia. In OAT (Occluded Artery Trial), there was no difference in the composite endpoint of death, reinfarction, or class IV HF at a median follow-up of 5.8 years between patients managed with PCI and those treated medically. Reinfarction rates tended to be higher in the PCI group.[380]

§Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

6.3. PCI of a Noninfarct Artery Before Hospital Discharge: Recommendations

Class I

1. **PCI is indicated in a noninfarct artery at a time separate from primary PCI in patients who have spontaneous symptoms of myocardial ischemia. (*Level of Evidence: C*)**

Class IIa

1. **PCI is reasonable in a noninfarct artery at a time separate from primary PCI in patients with intermediate- or high-risk findings on noninvasive testing.[216,232,233] (*Level of Evidence: B*)**

Multivessel coronary artery disease is present in 40% to 65% of patients presenting with STEMI who undergo primary PCI and is associated with adverse prognosis.[381,382] Studies of staged PCI of noninfarct arteries have been nonrandomized in design and have varied with regard to the timing of PCI and duration of follow-up. These variations have contributed to the disparate findings reported, although there seems to be a clear trend toward lower rates of adverse outcomes when primary PCI is limited to the infarct artery and PCI of a noninfarct artery is undertaken in staged fashion at a later time.[216,224,225,383,384] The largest of these observational studies compared 538 patients undergoing staged multivessel PCI within 60 days of primary PCI with propensity-matched individuals who had culprit-vessel PCI alone.[216] Multivessel PCI was associated with a lower mortality rate at 1 year (1.3% versus 3.3%; P=0.04). A nonsignificant trend toward a lower mortality rate at 1 year was observed in the subset of 258 patients who underwent staged PCI during the initial

Table 11. Adjunctive Antithrombotic Therapy to Support PCI After Fibrinolytic Therapy

	COR	LOE	References
Antiplatelet therapy			
Aspirin			
• 162- to 325-mg loading dose given with fibrinolytic agent (before PCI). (Section 5.1.4.1 and Table 7)	I	A	308, 330, 331
• 81- to 325-mg daily maintenance dose after PCI (indefinite)	I	A	253, 254, 257, 259, 330, 331
• 81 mg daily is the preferred daily maintenance dose	IIa	B	253, 259, 263, 264
$P2Y_{12}$ receptor inhibitors			
Loading doses			
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:			
• Continue clopidogrel 75 mg daily without an additional loading dose	I	C	260, 262, 330, 331
For patients who have not received a loading dose of clopidogrel:			
• If PCI is performed ≤24 h after fibrinolytic therapy: clopidogrel 300-mg loading dose before or at the time of PCI	I	C	N/A
• If PCI is performed >24 h after fibrinolytic therapy: clopidogrel 600-mg loading dose before or at the time of PCI	I	C	N/A
• If PCI is performed >24 h after treatment with a fibrin-specific agent or >48 h after a non–fibrin-specific agent: prasugrel 60 mg at the time of PCI	IIa	B	260, 262
For patients with prior stroke/TIA: prasugrel	III: Harm	B	260
Maintenance doses and duration of therapy			
DES placed: Continue therapy for at least 1 y with:			
• Clopidogrel: 75 mg daily	I	C	260, 262, 330, 331
• Prasugrel: 10 mg daily	IIa	B	260, 262
BMS placed: Continue therapy for at least 30 d and up to 1 y with:*			
• Clopidogrel: 75 mg daily	I	C	330, 331
• Prasugrel: 10 mg daily	IIa	B	260, 262
Anticoagulant therapy			
• Continue UFH through PCI, administering additional IV boluses as needed to maintain therapeutic ACT depending on use of GP IIb/IIIa receptor antagonist†	I	C	N/A
• Continue enoxaparin through PCI:	I	B	332, 390
◦ No additional drug if last dose was within previous 8 h			
◦ 0.3-mg/kg IV bolus if last dose was 8 to 12 h earlier			
• Fondaparinux:	III: Harm	C	304
◦ As sole anticoagulant for PCI			

*Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty after fibrinolysis alone according to the recommendations listed for BMS. (*Level of Evidence: C*)

†The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250-300 s (HemoTec device) or 300-350 s (Hemochron device).

ACT indicates activated clotting time; BMS, bare-metal stent; COR, Class of Recommendation; DES, drug-eluting stent; GP, glycoprotein; IV, intravenous; LOE, Level of Evidence; N/A, not available; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

hospitalization for STEMI.[216] Although fractional flow reserve is evaluated infrequently in patients with STEMI, at least 1 study suggests that determination of fractional flow reserve may be useful to assess the hemodynamic significance of potential target lesions in noninfarct arteries.[385] The writing committee encourages research into the benefit of PCI of noninfarct arteries in patients with multivessel disease after successful primary PCI (Section 12.6).

6.4. Adjunctive Antithrombotic Therapy to Support Delayed PCI After Fibrinolytic Therapy

See Table 11 for a summary of recommendations from this section.

The selection of adjunctive antiplatelet and anticoagulant therapies for use during PCI after fibrinolytic therapy should take into account the fibrinolytic agent used, the time since its administration, and the antiplatelet and anticoagulant agents already administered. GP IIb/IIIa inhibitors should be used with great caution, if at all, after full-dose fibrinolytic therapy, because this combination is associated with high rates of bleeding and ICH, particularly in the elderly.[386–388,389]

6.4.1. Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy: Recommendations

Class I

1. **After PCI, aspirin should be continued indefinitely.[253,254,257,259,330,331] (*Level of Evidence: A*)**
2. **Clopidogrel should be provided as follows:**
   a. **A 300-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI**

within 24 hours of receiving fibrinolytic therapy (*Level of Evidence: C*);

b. A 600-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy (*Level of Evidence: C*); and

c. A dose of 75 mg daily should be given after PCI.[260,262,330,331] (*Level of Evidence: C*)

Class IIa

1. **After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.[253,259,263,264] (*Level of Evidence: B*)**
2. **Prasugrel, in a 60-mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent.[260,262] (*Level of Evidence: B*)**
3. **Prasugrel, in a 10-mg daily maintenance dose, is reasonable after PCI.[260,262] (*Level of Evidence: B*)**

Class III: Harm

1. **Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.[260] (*Level of Evidence: B*)**

Patients with STEMI should receive clopidogrel at the time of administration of a fibrinolytic agent as a routine part of a pharmacological reperfusion strategy (Section 5.1). Clopidogrel then should be continued in uninterrupted fashion through and after PCI. The optimal loading dose of clopidogrel before or at the time of PCI in patients who may not have received it previously with fibrinolytic therapy is not known. In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis In Myocardial Infarction 28) trial,[331] PCI was performed 2 to 8 days after fibrinolysis in about half of the enrolled patients, and open-label clopidogrel (300-mg loading dose, 75-mg maintenance dose) was administered after diagnostic angiography in patients undergoing infarct artery stenting. Treatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI, or stroke (major secondary composite endpoint) after PCI. In addition, there was no significant increase in the rates of TIMI major or minor bleeding with clopidogrel treatment. A subset of patients with STEMI in the TRITON-TIMI 38 trial received fibrinolytic therapy >24 hours (for fibrin-specific agents) or >48 hours (for non–fibrin-specific agents) before PCI. In this subset, the use of prasugrel compared to clopidogrel was associated with a significantly lower rate of the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (HR: 0.65; 95% CI: 0.54 to 0.87; P=0.0017), and a similar rate of TIMI major bleeding unrelated to CABG.[262] Accordingly, prasugrel (60-mg loading dose) may be used as an alternative to clopidogrel in patients with STEMI who undergo delayed PCI after administration of a fibrinolytic agent.

6.4.2. Anticoagulant Therapy to Support PCI After Fibrinolytic Therapy: Recommendations

Class I

1. **For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with intravenous UFH, additional boluses of intravenous UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (*Level of Evidence: C*)**
2. **For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between 8 and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.[335,390] (*Level of Evidence: B*)**

Class III: Harm

1. **Fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered because of the risk of catheter thrombosis.[304] (*Level of Evidence: C*)**

Anticoagulation should be continued through emergent or nonurgent PCI procedures performed during the index hospitalization after initial use of fibrinolytic therapy. For patients who received UFH or enoxaparin with fibrinolytic therapy, these agents may be continued uninterrupted through the PCI procedure.[390] Transitioning from enoxaparin to either UFH or bivalirudin is possible, provided the last enoxaparin dose was >12 hours before PCI. Similarly, UFH may be transitioned to bivalirudin for PCI. Fondaparinux does not provide adequate anticoagulation for PCI, and additional intravenous boluses of UFH (or bivalirudin) should be administered.[304]

7. Coronary Artery Bypass Graft Surgery

7.1. CABG in Patients With STEMI: Recommendations

Class I

1. **Urgent CABG is indicated in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features.[391–393] (*Level of Evidence: B*)**
2. **CABG is recommended in patients with STEMI at time of operative repair of mechanical defects.[394–398] (*Level of Evidence: B*)**

Class IIa

1. **The use of mechanical circulatory support is reasonable in patients with STEMI who are hemodynamically unstable and require urgent CABG. (*Level of Evidence: C*)**

Class IIb

1. **Emergency CABG within 6 hours of symptom onset may be considered in patients with STEMI who do not have cardiogenic shock and are not candidates for PCI or fibrinolytic therapy. (*Level of Evidence: C*)**

CABG has a limited role in the acute phase of STEMI other than for cardiogenic shock, but it may be indicated for failed PCI, for coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect, such as ventricular septal, papillary muscle, or free-wall rupture. Older case series highlighted a potential excess mortality risk for CABG when performed early after STEMI, which was related to worsening myocardial injury from cardiopulmonary bypass, aortic cross-clamping, and cardioplegic arrest, with hemorrhagic transformation and infarct expansion. However, contemporary modifications to the standard operative approach, such as on-pump beating-heart surgery, off-pump techniques, or adjunctive temporary mechanical circulatory support devices, may lead to improved survival rates after CABG in the acute hospital phase.

7.2. Timing of Urgent CABG in Patients With STEMI in Relation to Use of Antiplatelet Agents: Recommendations

Class I

1. **Aspirin should not be withheld before urgent CABG.[399] (*Level of Evidence: C*)**
2. **Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent on-pump CABG, if possible.[400–404] (*Level of Evidence: B*)**
3. **Short-acting intravenous GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2 to 4 hours before urgent CABG.[405,406] (*Level of Evidence: B*)**
4. **Abciximab should be discontinued at least 12 hours before urgent CABG.[362] (*Level of Evidence: B*)**

Class IIb

1. **Urgent off-pump CABG within 24 hours of clopidogrel or ticagrelor administration might be considered, especially if the benefits of prompt revascularization outweigh the risks of bleeding.[401,407–409] (*Level of Evidence: B*)**
2. **Urgent CABG within 5 days of clopidogrel or ticagrelor administration or within 7 days of prasugrel administration might be considered, especially if the benefits of prompt revascularization outweigh the risks of bleeding. (*Level of Evidence: C*)**

In contrast to previous observations[410–412] of markedly increased rates of major bleeding and mediastinal reexploration after CABG in patients exposed to clopidogrel within 5 to 7 days before CABG, several reports have suggested that it might be reasonable to proceed with urgent surgery within a shorter time frame, especially when the benefits of revascularization outweigh the risks of bleeding, as often may be the case among patients with ACS.[402,404] Shorter delays to urgent surgery may also be possible when off-pump revascularization is planned. Among the 136 patients in CLARITY-TIMI 28 who underwent CABG within 5 days of clopidogrel exposure, there was no difference in the rates of major bleeding through 30 days of follow-up between the clopidogrel and placebo groups (7.5% versus 7.2%, respectively; P=1.00).[331] In a prospective RCT examining the effect of the timing of clopidogrel discontinuation before CABG, 3 groups were studied: clopidogrel continued to the day of surgery, clopidogrel discontinued 3 days before surgery, and clopidogrel discontinued 5 days before surgery. Patients in the continuation group experienced increased rates of bleeding and blood product utilization, but the 3- and 5-day discontinuation groups had comparably low bleeding rates and blood product usage that resembled historical control values.[413] In a retrospective analysis of a nonrandomized subgroup of patients in the PLATO trial, in which several definitions of bleeding were used, no significant differences in CABG-related bleeding were observed between patients allocated ticagrelor and patients who received clopidogrel, and there were no observed differences in the rates of reoperation.[401] In contrast, among the relatively few patients with STEMI in TRITON-TIMI 38 who underwent CABG during the 15-month course of the study, rates of TIMI major or minor bleeding after CABG were significantly higher with prasugrel than with clopidogrel (21.9% versus 4.1%; OR: 6.53; 95% CI: 1.78 to 23.94; P=0.0032).[262] The excess bleeding hazard observed with prasugrel should prompt consideration of an alternative antiplatelet strategy in patients with STEMI who may require urgent CABG during their index hospitalization. The timing of elective CABG in relation to the use of $P2Y_{12}$ receptor antagonists is referenced in Section 4.1 of the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery.[393]

8. Routine Medical Therapies

See Table 12 for a summary of selected routine medical therapies.

8.1. Beta Blockers: Recommendations

Class I

1. **Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: signs of HF, evidence of a low output state, increased risk for cardiogenic shock,‖ or other contraindications to use of oral beta blockers (PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).[414–416] (*Level of Evidence: B*)**
2. **Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.[417,418] (*Level of Evidence: B*)**

‖Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, systolic BP <120 mm Hg, sinus tachycardia >110 bpm or heart rate <60 bpm, and increased time since onset of symptoms of STEMI.

Table 12. Selected Routine Medical Therapies

Therapy	Indications	Dose/Administration	Avoid/Caution
Beta-Receptor Antagonists	• Oral: All patients without contraindication • IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Individualize: • Metoprolol tartrate 25 to 50 mg every 6 to 12 h orally, then transition over next 2 to 3 d to twice-daily dosing of metoprolol tartrate or to daily metoprolol succinate; titrate to daily dose of 200 mg as tolerated • Carvedilol 6.25 mg twice daily, titrate to 25 mg twice daily as tolerated • Metoprolol tartrate IV 5 mg every 5 min as tolerated up to 3 doses; titrate to heart rate and BP	• Signs of HF • Low output state • Increased risk of cardiogenic shock • Prolonged first-degree or high-grade AV block • Reactive airways disease
ACE Inhibitors	• For patients with anterior infarction, post-MI LV systolic dysfunction (EF ≤0.40) or HF • May be given routinely to all patients without contraindication	Individualize: • Lisinopril 2.5 to 5 mg/d to start; titrate to 10 mg/d or higher as tolerated • Captopril 6.25 to 12.5 mg 3 times/d to start; titrate to 25 to 50 mg 3 times/d as tolerated • Ramipril 2.5 mg twice daily to start; titrate to 5 mg twice daily as tolerated • Trandolapril test dose 0.5 mg; titrate up to 4 mg daily as tolerated	• Hypotension • Renal failure • Hyperkalemia
ARB	• For patients intolerant of ACE inhibitors	• Valsartan 20 mg twice daily to start; titrate to 160 mg twice daily as tolerated	• Hypotension • Renal failure • Hyperkalemia
Statins	• All patients without contraindications	• High-dose atorvastatin 80 mg daily	• Caution with drugs metabolized via *CYP3A4,* fibrates • Monitor for myopathy, hepatic toxicity • Combine with diet and lifestyle therapies • Adjust dose as dictated by targets for LDL cholesterol and non–HDL cholesterol reduction
Nitroglycerin	• Ongoing chest pain • Hypertension and HF	• 0.4 mg sublingual every 5 min up to 3 doses as BP allows • IV dosing to begin at 10 mcg/min; titrate to desired BP effect	• Avoid in suspected RV infarction • Avoid with SBP <90 mm Hg or if SBP >30 mm Hg below baseline • Avoid if recent (24 to 48 h) use of 5′-phosphodiesterase inhibitors
Oxygen	• Clinically significant hypoxemia (oxygen saturation <90%) • HF • Dyspnea	• 2 to 4 L/min via nasal cannula • Increase rate or change to face mask as needed	• Caution with chronic obstructive pulmonary disease and CO_2 retention
Morphine	• Pain • Anxiety • Pulmonary edema	• 4 to 8 mg IV initially, with lower doses in elderly • 2 to 8 mg IV every 5 to 15 min if needed	• Lethargic or moribund patient • Hypotension • Bradycardia • Known hypersensitivity

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CO_2, carbon dioxide; EF, ejection fraction; HDL, high-density lipoprotein; HF, heart failure; IV, intravenous; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; RV, right ventricular; and SBP, systolic blood pressure.

3. **Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility. (*Level of Evidence: C*)**

Class IIa

1. **It is reasonable to administer intravenous beta blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.[414–416] (*Level of Evidence: B*)**

The efficacy and safety of the early routine use of intravenous beta blockers were examined in COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial).[414] Early intravenous metoprolol followed by high-dose oral therapy had a neutral effect on the combined endpoint of death, recurrent MI, or cardiac arrest. There were lower rates of recurrent MI and VF in the treated group, outcomes that were balanced by a significantly higher rate of cardiogenic shock with metoprolol, especially on days 0 and 1. The likelihood of developing cardiogenic shock was increased in certain subgroups, including patients with age >70 years,

systolic BP <120 mm Hg, presenting heart rate >110 bpm, or increased time since onset of symptoms of STEMI. The benefit of beta blockers for secondary prevention has been established in numerous trials conducted in the prereperfusion era and appears to be greatest for patients with MI complicated by HF, LV dysfunction, or ventricular arrhythmias.[418] The long-term duration of routine beta-blocker therapy after uncomplicated MI in patients without HF or hypertension has not been prospectively addressed. AHA/ACCF secondary prevention guidelines recommend a 3-year treatment course in this patient subset.[257]

8.2. Renin-Angiotensin-Aldosterone System Inhibitors: Recommendations

Class I

1. **An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) less than or equal to 0.40, unless contraindicated.[420–423] (Level of Evidence: A)**
2. **An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors.[424,425] (*Level of Evidence: B*)**
3. **An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta blocker and who have an EF less than or equal to 0.40 and either symptomatic HF or diabetes mellitus.[426] (*Level of Evidence: B*)**

Class IIa

1. **ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use.[427–429] (*Level of Evidence: A*)**

Oral ACE inhibitors reduce fatal and nonfatal major cardiovascular events in patients with STEMI.[360,361,420,422,428–430] Their protective effects have been demonstrated independent of the use of other pharmacotherapies (ie, fibrinolytics, aspirin, and beta blockers). The magnitude of clinical benefit is greatest in high-risk patient subgroups (ie, anterior MI, EF ≤0.40, HF, prior MI, and tachycardia).[431] Demonstration of an early benefit (within the first 24 hours) supports the prompt use of these agents in patients without existing contraindications (hypotension, shock, bilateral renal artery stenosis or history of worsening of renal function with ACE inhibitor/ARB exposure, renal failure, or drug allergy). The role of routine long-term ACE inhibitor therapy in low-risk patients after STEMI who have been revascularized and treated with aggressive lipid-lowering therapies is less certain.[432] ARBs are indicated for ACE inhibitor–intolerant patients. Specifically, valsartan was found to be noninferior to captopril in the VALIANT (Valsartan in Acute Myocardial Infarction) trial.[424]

The EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) study established the benefit of an aldosterone antagonist, eplerenone, added to optimal medical therapy in eligible patients (creatinine ≤2.5 mg/dL in men and ≤2.0 mg/dL in women, potassium ≤5.0 mEq/L) 3 to 14 days after STEMI with EF ≤0.40 and either symptomatic HF or diabetes mellitus.[426] A post hoc analysis of the EPHESUS trial suggested a time-dependent treatment effect of eplerenone. Earlier initiation of the drug (<7 days) significantly reduced the rates of all-cause mortality, sudden cardiac death (SCD), and cardiovascular mortality/hospitalization, whereas initiation ≥7 days had no significant effect on outcomes.[433]

8.3. Lipid Management: Recommendations

Class I

1. **High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.[434–436] (*Level of Evidence: B*)**

Class IIa

1. **It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation. (*Level of Evidence: C*)**

Treatment with statins in patients stabilized after an ACS, including STEMI, lowers the risk of coronary heart disease death, recurrent MI, stroke, and the need for coronary revascularization.[437,438] More intensive statin therapy, compared with less intensive therapy, appears to be associated with an additional lowering of nonfatal clinical endpoints.[434,436,439] Among currently available statins, only high-dose atorvastatin (80 mg daily) has been shown to reduce death and ischemic events among patients with ACS.[436,440] Approximately one third of patients in the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) trial had STEMI.[436] Cardiovascular event rates were not significantly reduced with a tiered strategy of simvastatin (40 mg daily for 1 month followed by 80 mg daily) in the A to Z Trial (Aggrastat to Zocor),[439] and concerns have been raised recently about the safety of high-dose simvastatin (ie, 80 mg daily).[441] Although the benefit of high-intensity statins declines among statin-naïve patients with ACS as a function of decreasing low-density lipoprotein levels,[442] the writing committee recommends the use of statins in all patients with STEMI.[435] Statin therapy after ACS is beneficial even in patients with baseline low-density lipoprotein cholesterol levels <70 mg/dL.[443] Trials of statin therapy in patients with ACS and stable ischemic heart disease have been designed to compare either more intensive versus less intensive statin treatment or active statin versus placebo.[434–440] They have not been designed to compare clinical outcomes as a function of the specific low-density lipoprotein cholesterol level achieved with treatment. Improved compliance with therapy is a strong rationale for timing the initiation of lipid-lowering drug therapy before discharge after STEMI. Longer-term lipid management after STEMI, including indications for targeting triglycerides and non–high-density lipoprotein cholesterol, are addressed in the

"AHA/ACC Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Vascular Disease: 2011 Update."[257]

8.4. Nitrates

Although nitroglycerin can ameliorate symptoms and signs of myocardial ischemia by reducing LV preload and increasing coronary blood flow, it generally does not attenuate the myocardial injury associated with epicardial coronary artery occlusion unless vasospasm plays a significant role. Intravenous nitroglycerin may be useful to treat patients with STEMI and hypertension or HF. Nitrates should not be given to patients with hypotension, marked bradycardia or tachycardia, RV infarction, or 5'phosphodiesterase inhibitor use within the previous 24 to 48 hours.[444] There is no role for the routine use of oral nitrates in the convalescent phase of STEMI.

8.5. Calcium Channel Blockers

An overview of 28 RCTs involving 19 000 patients demonstrated no beneficial effect on infarct size or the rate of reinfarction when calcium channel blocker therapy was initiated during either the acute or convalescent phase of STEMI.[445] Calcium channel blockers may be useful, however, to relieve ischemia, lower BP, or control the ventricular response rate to atrial fibrillation (AF) in patients who are intolerant of beta blockers. Caution is advised in patients with LV systolic dysfunction. The use of the immediate-release nifedipine is contraindicated in patients with STEMI because of hypotension and reflex sympathetic activation with tachycardia.[446]

8.6. Oxygen

Few data exist to support or refute the value of the routine use of oxygen in the acute phase of STEMI, and more research is needed. A pooled Cochrane analysis of 3 trials showed a 3-fold higher risk of death for patients with confirmed acute MI treated with oxygen than for patients with acute MI managed on room air. Oxygen therapy is appropriate for patients who are hypoxemic (oxygen saturation <90%) and may have a salutary placebo effect in others. Supplementary oxygen may, however, increase coronary vascular resistance.[447] Oxygen should be administered with caution to patients with chronic obstructive pulmonary disease and carbon dioxide retention.

8.7. Analgesics: Morphine, Nonsteroidal Anti-Inflammatory Drugs, and Cyclooxygenase II Inhibitors

In the absence of a history of hypersensitivity, morphine sulfate is the drug of choice for pain relief in patients with STEMI, especially those whose course is complicated by acute pulmonary edema. It can alleviate the work of breathing, reduce anxiety, and favorably affect ventricular loading conditions. The dose of morphine sulfate needed to achieve adequate pain control will vary depending on patient age, body size, BP, and heart rate. Naloxone can be administered in doses of 0.1 to 0.2 mg IV every 15 minutes when indicated to reverse the narcotic effects of morphine, and atropine 0.5 to 1.5 mg IV may be administered to counter excessive morphine-related bradycardia.

Epidemiological studies and retrospective analyses of RCTs have suggested that nonsteroidal anti-inflammatory drugs and selective cyclooxygenase II enzyme (COX-2) inhibitors may be associated with an increased risk of death, reinfarction, cardiac rupture, hypertension, renal insufficiency, and HF.[448–451] Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors are contraindicated in patients with STEMI. They should not be initiated in the acute phase and should be discontinued in patients using them before hospitalization.

9. Complications After STEMI

9.1. Cardiogenic Shock

9.1.1. Treatment of Cardiogenic Shock: Recommendations

Class I

1. **Emergency revascularization with either PCI or CABG is recommended in suitable patients with cardiogenic shock due to pump failure after STEMI irrespective of the time delay from MI onset.[212,379,452] (*Level of Evidence: B*)**
2. **In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG.[81,453,454] (*Level of Evidence: B*)**

Class IIa

1. **The use of intra-aortic balloon pump (IABP) coun-terpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.[455–459] (*Level of Evidence: B*)**

Class IIb

1. **Alternative LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock. (*Level of Evidence: C*)**

Cardiogenic shock in patients with STEMI may be caused by extensive LV infarction or by mechanical complications, including papillary muscle rupture, ventricular septal rupture, free-wall rupture with tamponade, and RV infarction. The onset of cardiogenic shock due to mechanical complications after STEMI is bimodal; most cases occur within 24 hours. For those with pump failure, 15% of cases occur at time of presentation, and 85% develop during hospitalization. Revascularization with timely PCI or CABG is the preferred reperfusion strategy for patients with STEMI and shock due to pump failure, irrespective of the time delay. Shock or severe HF is perhaps the only clinical scenario in which acute revascularization of significant stenoses in noninfarct arteries can be justified. In the SHOCK trial, mortality rates at 6 and 1 year were significantly lower in patients allocated to emergency revascularization than in patients who received immediate medical stabilization.[212,354] Nearly two thirds of the patients in the medical stabilization group received

fibrinolytic therapy, and 25% underwent delayed revascularization. IABP support was used in 86% of both groups. Although the trial did not show benefit with emergency revascularization for the prespecified age group >75 years, the small number of patients in the trial did not allow for firm conclusions to be drawn about management. Elderly patients offered emergency revascularization in the nonrandomized SHOCK registry had a substantial adjusted survival benefit with emergency revascularization compared with delayed or no revascularization.[460] Similar findings in favor of early revascularization for selected elderly patients were reported from 2 additional registries.[461,462] Although age alone is not a contraindication to emergency revascularization in this setting, individual judgment based on comorbidities, functional status, and patient directives is necessary in the elderly. Triage and immediate transfer to a PCI-capable facility with on-site cardiac surgical backup are indicated for patients with STEMI complicated by shock. Fibrinolytic therapy is reserved for patients without contraindications within 24 hours of MI for whom revascularization is considered not feasible for technical, anatomic, or patient-related issues. The need for hemodynamic support with inotropic therapy, IABP, or both should be assessed on an individual basis. Observational data on the usefulness of IABP in this setting are conflicting. A meta-analysis supports IABP therapy as an adjunct to fibrinolysis but not to primary PCI.[458] Compared with IABP, LV assist devices may provide superior hemodynamic support and serve as more effective bridges to recovery or transplantation, though experience with their use in this setting is limited.[463,464] Medical support with inotropes and vasopressor agents should be individualized and guided by invasive hemodynamic monitoring. Use of dopamine in this setting may be associated with excess hazard.[465]

9.2. Severe HF

The development of HF after STEMI is an indication for angiography with intent to proceed with revascularization if not previously performed. LV myocardium may be ischemic, stunned, hibernating, or irrevocably injured, and viability assessment may be needed depending on the timing of revascularization. Ischemic (functional) mitral regurgitation due to LV remodeling may coexist, progress over time, and require surgical attention depending on its severity. Medical treatment is based on the use of diuretics, vasodilators, and inotropic agents when required. Inhibitors of the renin-angiotensin-aldosterone system should be provided as tolerated, and the indications for beta-blocker therapy should be evaluated continuously throughout the hospital course.

9.3. RV Infarction

RV infarction complicates the course of approximately one third of patients with inferior STEMI, is most often due to proximal occlusion of the right coronary artery, and is associated with a higher mortality risk. Evidence of RV involvement should be sought in all patients with inferior STEMI. The clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure is characteristic. Demonstration of 1-mm ST elevation in lead V1 and in right precordial lead V_4R is the most sensitive ECG marker of RV injury.[466] Transthoracic echocardiography can be helpful in patients with initially nondiagnostic findings.[467] Treatment includes maintenance of RV preload, reduction of RV afterload, inotropic support if needed, and immediate reperfusion.[468,469] Nitrates and diuretics should be avoided. Restoration of atrioventricular (AV) synchrony or cardioversion from AF may be needed.

9.4. Mechanical Complications

9.4.1. Diagnosis

Mechanical complications after STEMI have a bimodal, temporal distribution: Most occur in the first 24 hours, and the remainder present within the first week. The presence of a new systolic murmur indicates the possibility of either ventricle septal rupture or mitral regurgitation. Diagnosis usually can be established with transthoracic echocardiography. Surgical consultation should be obtained when a mechanical defect is suspected. Prompt repair (with or without CABG) is indicated in most cases. IABP can provide temporary circulatory support.

9.4.2. Mitral Regurgitation

Mitral regurgitation after STEMI occurs via 1 of 2 mechanisms: papillary muscle rupture or postinfarction LV remodeling with displacement of the papillary muscles, leaflet tethering, and annular dilatation. Acute rupture affects the posteromedial papillary muscle more often than anterolateral papillary muscle because of its singular blood supply.[470,471] Acute severe mitral regurgitation is characterized by pulmonary edema and/or shock; a systolic murmur may not always be appreciated. Suitable patients with papillary muscle rupture should be considered for urgent surgery while temporary stabilization with medical therapy and IABP is attempted. Mitral valve replacement rather than repair usually is required in this setting. Although emergency mitral valve replacement is associated with a relatively high mortality rate (20%), survival and ventricular function are improved with surgery compared with medical therapy alone. Delay to operation appears to increase the risk of further myocardial injury, organ failure, and death.[472] Five-year survival rates after surgery average 60% to 70%.[397,473–476]

With ischemic (functional) mitral regurgitation, treatment is focused on timely reperfusion, diuretics, and afterload reduction. The severity of mitral regurgitation may improve in some patients with aggressive medical treatment, PCI, or both. The rate of long-term survival after STEMI declines as a function of residual mitral regurgitation severity. If surgery is required during the index hospitalization because of ongoing ischemia or HF, mitral valve repair with a downsized annuloplasty ring usually is performed, though valve replacement may be preferred in many cases. In this regard, management of ischemic mitral regurgitation differs importantly from that of myxomatous mitral regurgitation.

9.4.3. Ventricular Septal Rupture

Ventricular septal rupture usually is heralded by a loud systolic murmur and HF or shock, depending on the size of the defect and the degree of RV and LV dysfunction. Data from the GUSTO-1 (The Global Use of Strategies to Open Occluded Coronary Arteries) trial and the SHOCK registry

indicate that ventricular septal rupture occurs most often within the first 24 hours in patients with STEMI treated with fibrinolytic therapy.[477,478] Emergency surgical repair is necessary, even in hemodynamically stable patients,[479–481] because the rupture site can expand abruptly, resulting in sudden hemodynamic collapse in previously stable patients.[481] Temporizing medical treatment consists of inotropic and vasodilator agents, with IABP when needed. The surgical mortality rate remains high, especially among patients with shock, ranging from 20% to 87% in reported series.[395,477–480,482,483] Mortality risk is higher for patients with inferior-basal defects than for those with anterior-apical defects. Percutaneous closure is a less invasive option that might allow for initial hemodynamic stabilization, but experience with this approach is limited, and residual shunts are common. Further technical developments and prospective trials are required to identify patients best suited for transcatheter closure.

9.4.4. LV Free-Wall Rupture

Free-wall rupture is characterized by recurrent chest pain and ST-T-wave changes, with rapid progression to hemodynamic collapse, electromechanical dissociation, and death.[484] It is observed most frequently in patients with first MI, anterior infarction, the elderly, and women. Other risk factors include hypertension during the acute phase of STEMI, lack of antecedent angina or prior MI, absence of collateral blood flow, Q waves on ECG, use of corticosteroids or nonsteroidal anti-inflammatory drugs, and administration of fibrinolytic therapy >14 hours after symptom onset.[485,486] Pseudoaneurysm formation with contained rupture and tamponade can be recognized with transthoracic echocardiography, and emergency surgery should be considered. Most case series of patients reaching the operating room for management of this complication are of small size, with mortality rates approaching 60%.[396,487]

9.4.5. LV Aneurysm

Ventricular aneurysm formation after STEMI occurs in <5% of patients and is more frequent in those with anterior infarction. Incidence rates have declined with timely reperfusion. Surgery for LV aneurysm after STEMI is rarely needed but may be considered for treatment of HF, ventricular arrhythmias not amenable to drugs or radiofrequency ablation, or recurrent thromboembolism despite appropriate anticoagulant therapy.

9.5. Electrical Complications During the Hospital Phase of STEMI

9.5.1. Ventricular Arrhythmias

Ventricular arrhythmias are common early after onset of STEMI, and not all require intervention. Out-of-hospital cardiac arrest with STEMI is most often due to lethal ventricular arrhythmias, including sustained VT and VF (Section 3.6.1). The mechanisms for these arrhythmias are multifactorial and include ongoing ischemia, hemodynamic and electrolyte abnormalities, reentry, and enhanced automaticity. As many as 10% of hospitalized patients receiving fibrinolytic therapy in the GUSTO-I trial had sustained VT/VF complicating their course.[488] An analysis of patients referred for primary PCI in the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial reported a lower incidence of sustained VT/VF (5.7%); 90% of cases occurred within 48 hours of presentation.[489] Compared with patients without VT/VF, 90-day mortality risk was 2-fold higher for patients with early VT/VF (ie, before the completion of primary PCI) and 5-fold higher for patients with late VT/VF (ie, after primary PCI). Several factors were associated with the occurrence of both early and late VT/VF, including HF, hypotension, tachycardia, shock, and TIMI flow grade. Treatment consists of immediate defibrillation or cardioversion for VF or pulseless sustained VT, respectively, and antiarrhythmic drug therapy in accordance with the 2010 Advanced Cardiac Life Support guidelines for sustained VT with a pulse.[490] Prevention of VT/VF is directed to correction of electrolyte and acid/base abnormalities, optimization of myocardial perfusion, eradication of ongoing ischemia, and treatment of associated complications such as HF or shock. Early (within 24 hours of presentation) administration of beta blockers has been associated with a reduction in the incidence of VF[414,489] and is recommended for all patients without contraindications (Section 8.1). The prophylactic use of lidocaine is not recommended. Premature ventricular complexes, nonsustained VT not associated with hemodynamic compromise, and accelerated idioventricular rhythms that emerge after reperfusion are not indicative of increased SCD risk and do not require specific therapy in the acute phase of STEMI.

9.5.2. Implantable Cardioverter-Defibrillator Therapy Before Discharge

Class I

1. **Implantable cardioverter-defibrillator (ICD) therapy is indicated before discharge in patients who develop sustained VT/VF more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.[491–493] (*Level of Evidence: B*)**

Life-threatening ventricular arrhythmias that occur >48 hours after STEMI usually are associated with significant LV systolic dysfunction and signify poor prognosis. Although previous RCTs[492,494,495] have not specifically addressed this population of patients with STEMI, they have shown clear and consistent benefit of ICD therapy for survivors of sustained VT or VF arrest.[493] In the absence of a reversible cause, late (>48 hours) in-hospital sustained VT/VF is an indication for ICD therapy for secondary prevention of SCD. For other at-risk patients, particularly those with significantly reduced left ventricular ejection fraction (LVEF), candidacy for ICD therapy for primary prevention of SCD should be reassessed at ≥40 days after discharge (Section 10.3). See the "2008 ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities."[496]

9.5.3. AF and Other Supraventricular Tachyarrhythmias

AF, atrial flutter, and other supraventricular tachyarrhythmias occur frequently in patients with STEMI and are triggered by excessive sympathetic stimulation, atrial stretch due to LV or

RV volume/pressure overload, atrial infarction, pericarditis, electrolyte abnormalities, hypoxia, or underlying lung disease. By far the most common supraventricular arrhythmia is AF, which occurs in 8% to 22% of patients with STEMI, with higher rates in elderly patients and those with HF and hypertension. In a contemporary study, the incidence of new-onset AF during hospitalization was 6.3%.[497] New-onset AF was significantly associated with shock, HF, stroke, and 90-day mortality.[497] These observations mirrored those seen in earlier trials.[317,422,428,497–499] The cumulative incidence of AF among MI survivors with EF ≤0.40 over approximately 2 years of follow-up approaches 30%.[500]

Management of AF during hospitalization for STEMI is based on the usual considerations of rhythm versus rate control and the indications for anticoagulation according to current guidelines.[501,502] For hemodynamically unstable patients or those with ongoing ischemic symptoms, treatment should be implemented according to the 2010 Advanced Cardiac Life Support guideline for management of unstable supraventricular tachyarrhythmias.[490] If medical treatment is unsuccessful, synchronized, direct current cardioversion may be indicated. Provision of anticoagulation in the context of DAPT creates additional challenges related to the risk of bleeding (Section 9.7).

9.5.4. Bradycardia, AV Block, and Intraventricular Conduction Defects

9.5.4.1. Pacing in STEMI: Recommendation

Class I

1. **Temporary pacing is indicated for symptomatic bradyarrhythmias unresponsive to medical treatment. (*Level of Evidence: C*)**

Sinus bradycardia is common early after STEMI, particularly with inferior location. It is mediated through increased vagal tone, is usually self-limited, and generally requires no treatment. It may be necessary to withhold beta blockers until the bradycardia resolves. Symptomatic or hemodynamically important sinus bradycardia should be treated with atropine or temporary pacing if not responsive.[504]

The development of AV block and intraventricular conduction delays is associated with the extent of infarction. The incidence of abnormal conduction has decreased substantially in the reperfusion era. In a survey of nearly 3 million hospital discharges after MI from 1996 to 2003, the incidence of complete heart block was 3.7% in inferior/posterior MI and 1.0% in anterior/lateral MI.[505] AV block of varying degree and persistent bundle-branch block develop in approximately 7% and 5% of patients with STEMI, respectively.[506,507] High-grade (ie, second- or third-degree) AV block and persistent bundle-branch block are independently associated with worse short- and long-term prognosis in both inferior/posterior and anterior/lateral MI but are more ominous in anterior/lateral MI because of a relatively greater extent of myocardial injury.[506–508]

First-degree AV block does not require treatment. High-grade AV block with inferior/posterior STEMI usually is transient and associated with a narrow complex/junctional escape rhythm that can be managed conservatively. Application of transcutaneous pacing pads for potential use is reasonable. Prophylactic placement of a temporary pacing system is recommended for high-grade AV block and/or new bundle-branch (especially LBBB) or bifascicular block in patients with anterior/lateral MI. Choice of pacing system (transcutaneous versus transvenous) varies across institutions. Indications for permanent pacing for persistent AV block or bundle-branch block after STEMI are reviewed in the 2008 ACC/AHA/HRS device-based therapy guidelines.[496]

9.6. Pericarditis

9.6.1. Management of Pericarditis After STEMI: Recommendations

Class I

1. **Aspirin is recommended for treatment of pericarditis after STEMI.[509] (*Level of Evidence: B*)**

Class IIb

1. **Administration of acetaminophen, colchicine, or narcotic analgesics may be reasonable if aspirin, even in higher doses, is not effective. (*Level of Evidence: C*)**

Class III: Harm

1. **Glucocorticoids and nonsteroidal anti-inflammatory drugs are potentially harmful for treatment of pericarditis after STEMI.[510,511] (*Level of Evidence: B*)**

The incidence of acute pericarditis after STEMI has decreased with the aggressive use of reperfusion therapy.[512,513] Pericarditis should be considered in the differential diagnosis of recurrent chest pain after STEMI, particularly when the discomfort is pleuritic or positional, radiates to the trapezius ridge, and is associated with a pericardial friction rub. Recurrent or worsening ST elevation without early T-wave inversion may be present. Distinction from reinfarction or acute stent thrombosis is crucial. In rare circumstances, if pain is persistent (>1 week) and accompanied by systemic features of malaise, fever, and increased inflammatory biomarkers, Dressler syndrome should be considered. In most cases, the pain is self-limited and responds to conservative measures. The use of colchicine has been extrapolated from its efficacy in other settings. Although pericarditis is not an absolute contraindication to anticoagulation,[514] caution should be exercised because of the potential for hemorrhagic conversion.[515]

Asymptomatic pericardial effusions are common after STEMI.[516,517] It is important to exclude free-wall rupture when a pericardial effusion is present,[518,519] especially if the

width of the effusion is >1 cm.[520] When tamponade is present, free-wall rupture, hemorrhagic conversion, or aortic dissection should be considered. Anticoagulation should be discontinued in the presence of a significant (≥1 cm) or enlarging pericardial effusion.

9.7. Thromboembolic and Bleeding Complications

9.7.1. Thromboembolic Complications

9.7.1.1. Anticoagulation: Recommendations¶

Class I

1. **Anticoagulant therapy with a vitamin K antagonist should be provided to patients with STEMI and AF with CHADS2 score# greater than or equal to 2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder. (*Level of Evidence: C*)**
2. **The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding.** (*Level of Evidence: C*)**

Class IIa

1. **Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi. (*Level of Evidence: C*)**

Class IIb

1. **Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis. (*Level of Evidence: C*)**
2. **Targeting vitamin K antagonist therapy to a lower international normalized ratio (eg, 2.0 to 2.5) might be considered in patients with STEMI who are receiving DAPT. (*Level of Evidence: C*)**

Previous recommendations for the use of vitamin K antagonists, either alone or in combination with low-dose aspirin, for secondary prevention or for reducing the risk of systemic thromboembolism after STEMI, must be reconsidered in the era of DAPT.[4,48] The availability of several $P2Y_{12}$ receptor inhibitors has virtually eliminated the former reliance on vitamin K antagonists as an alternative to aspirin for aspirin-allergic patients. A meta-analysis of RCTs comparing warfarin plus aspirin to aspirin alone in patients with ACS showed that in studies with an international normalized ratio goal of 2.0 to 3.0, combination therapy was associated with a significant reduction in major adverse events at the expense of an increased risk of major bleeding.[521] None of the trials included patients treated with primary PCI or DAPT.

Triple therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor should be restricted to specific clinical situations after STEMI in which the risk of systemic or venous thromboembolism or stent thrombosis is considered to exceed that of bleeding. Patient preferences and values should be taken into consideration, because individuals may weigh these outcomes differently. The novel oral anticoagulants such as dabigatran have not been evaluated in this context, and thus no recommendation for their use can be made. The duration of vitamin K antagonist therapy can be limited to 3 months in patients with or at risk for LV thrombus (eg, those with anteroapical akinesis or dyskinesis), whereas the duration of DAPT could be predicated on stent type or whether STEMI treatment included a stent.[219,522,523] For patients undergoing primary PCI who require anticoagulation, avoidance of a DES is strongly preferred. When triple therapy is used, an international normalized ratio targeted to a range of 2.0 to 2.5 might be reasonable, though prospective data are lacking. Use of DAPT alone with aspirin and clopidogrel also might be considered for patients with STEMI who have AF and low to intermediate CHADS2 scores (0 to 1), with reconsideration of the indications for anticoagulation over time.[296,522]

The incidence of venous thromboembolic events after STEMI has declined significantly,[526] though patients with HF or on prolonged bed rest remain at risk.[527] The approach to the prevention and treatment of venous thromboembolic disease during hospitalization, with both pharmacological and mechanical measures, is similar to that for other critically ill patients.[528]

9.7.1.2. Heparin-Induced Thrombocytopenia

HIT, with or without associated thrombosis, can infrequently complicate the course of patients with ACS,[529] particularly patients who previously have been exposed to heparin or who receive heparin over several hospital days. From 1% to 5% of all patients receiving heparin will develop HIT, and of these, 25% to 50% will develop thrombotic complications. In the CATCH (Complications After Thrombocytopenia Caused by Heparin) registry,[530,531] thrombocytopenia was common among those who received heparin for >96 hours (36.4%) and was associated with a significantly increased risk of death, MI, or HF. Recognition of HIT frequently was delayed, and treatment often did not include a direct thrombin inhibitor. Data on the use of direct thrombin inhibitors in patients with STEMI who develop HIT are limited.[532,533] For patients with STEMI and HIT who require stenting, bivalirudin would be the preferred anticoagulant. Management of patients with HIT who require urgent CABG can be more difficult.[534]

9.7.2. Bleeding Complications

Despite variable definitions for major and minor bleeding used in clinical trials, bleeding that complicates the course of an ACS, including STEMI, is independently associated with recurrent MI, stroke, death, longer hospital stay, and increased cost. The risk of death increases as a function of the severity of bleeding, independent of the success or failure of reperfusion therapy. In a pooled analysis from 4 ACS trials, the adjusted hazard ratio for death within 30 days ranged from 1.6 with mild bleeding to 10.6 with severe bleeding.[535] Most bleeding is procedure related, although gastrointestinal and intracerebral bleeding may be more life threatening. Factors likely to contribute to adverse outcomes with ACS-related

¶These recommendations apply to patients who receive intracoronary stents during PCI for STEMI. Among individuals with STEMI who do not receive an intracoronary stent, the duration of DAPT beyond 14 days has not been studied adequately for patients who undergo balloon angioplasty alone, are treated with fibrinolysis alone, or do not receive reperfusion therapy. In this subset of patients with STEMI who do not receive an intracoronary stent, the threshold for initiation of oral anticoagulation for secondary prevention, either alone or in combination with aspirin, may be lower, especially if a shorter duration (ie, 14 days) of DAPT is planned.[521]

#CHADS2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack [doubled risk weight]) score.

**Individual circumstances will vary and depend on the indications for triple therapy and the type of stent placed during PCI. After this initial treatment period, consider therapy with a vitamin K antagonist plus a single antiplatelet agent. For patients treated with fibrinolysis, consider triple therapy for 14 days, followed by a vitamin K antagonist plus a single antiplatelet agent.[522–525]

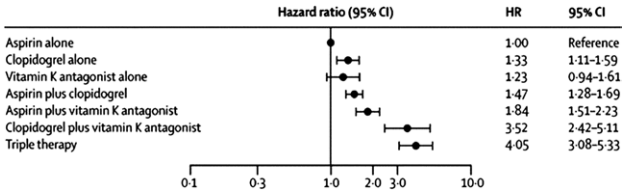

Figure 4. Adjusted risk of nonfatal and fatal bleeding in patients treated with aspirin, clopidogrel, and/or vitamin K antagonists after first MI. Compared with aspirin alone, triple therapy is associated with a 3- to 4-fold increased risk of fatal and nonfatal bleeding. CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction. Adapted with permission from Sørensen et al.[533]

bleeding include patient comorbidities,[536,537] discontinuation of antiplatelet or anticoagulant therapy in response to bleeding,[536,538] and blood transfusion.[539,540] Additional considerations include types of antiplatelet or anticoagulant agent at time of PCI,[248,541,542] number of antithrombotic agents used,[533] dosing,[543] duration of therapy, crossover from low-molecular-weight heparin to UFH, HF or shock, diabetes mellitus, peripheral artery disease, and prior warfarin use. If triple antithrombotic therapy is required after discharge, the risk of bleeding increases (Figure 4).[533]

Risk factors for bleeding in patients with ACS have been identified from several clinical trials[535,544–546] (Table 13). Predictive models for major bleeding in patients with ACS and in patients undergoing PCI have been reported from the NCDR ACTION Registry–GWTG.[547,548] An analysis from the ACTION Registry–GWTG suggests that the CRUSADE bleeding risk score, developed in patients with non–ST-elevation MI, may be extended to the STEMI population.[549] Major bleeding occurred in 2.8% of >40 000 patients with acute MI in the GRACE Registry.[536] Patients who experienced a major bleeding episode were more likely to die in hospital than were those who did not bleed (20.9% versus 5.6%; $P<0.001$), even after adjustment for several relevant demographic and clinical variables. One in 5 patients with a major bleed did not survive to hospital discharge; these patients accounted for 10% of all hospital deaths and were older, more severely ill, and more likely to undergo invasive procedures. In ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis In Myocardial Infarction 25), high 30-day mortality rates after major bleeding in patients with STEMI treated with fibrinolysis and either unfractionated or low-molecular-weight heparin were driven largely by the very poor prognosis associated with ICH (65% mortality rate).[537] The overall incidence of ICH in this study was 0.6%.[332] The relationship between non-ICH bleeding and death in both ExTRACT-TIMI 25 and TRITON-TIMI 38 may have been confounded by patient attributes, severity of illness, and treatment protocols.[537,550] To minimize the risk of bleeding complications, an assessment of patient, procedural, and pharmacological risk factors should be performed at time of presentation with STEMI and continuously thereafter. As an example, a longer time to PCI may be justifiable if the risk of hemorrhage with fibrinolysis is considered prohibitive.

Table 13. Selected Risk Factors for Bleeding in Patients With ACS

Advanced age (>75 y)
Female sex
HF or shock
Diabetes mellitus
Body size
History of GI bleeding
Presentation with STEMI or NSTEMI (vs UA)
Severe renal dysfunction (CrCl <30 mL/min)
Elevated white blood cell count
Anemia
Use of fibrinolytic therapy
Invasive strategy
Inappropriate dosing of antithrombotic medications
Chronic oral anticoagulant therapy

ACS indicates acute coronary syndrome; CrCl, creatinine clearance; GI, gastrointestinal; HF, heart failure; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; and UA, unstable angina. [553,554,543,547]

Evidence suggests that although anemia is a risk factor for bleeding, the threshold for transfusion should be high.[551] Absent ongoing ischemia, transfusion should be avoided unless the hemoglobin level is <8 mg/dL. The optimal hemoglobin level in the transfused patient is not known, but the number of units provided should be minimized.[539,552]

9.7.2.1. Treatment of ICH

Older age, female sex, low body weight (<70 kg [female] and <80 kg [male]), prior stroke, and hypertension on presentation (with a graded increase beginning at >160 to 170 mm Hg systolic) are the major risk factors for ICH. Once ICH is recognized, all antiplatelet and anticoagulant therapy should be stopped. Brain imaging with emergency neurological and neurosurgical consultation is required. Consideration can be given to the use of protamine, fresh frozen plasma, prothrombin complex concentrates, activated factor VII,[555] and platelets as indicated. Resumption and timing of anticoagulant and/or antiplatelet therapy after ICH should be individualized and guided by neurosurgical consultation.[556]

9.7.2.2. Vascular Access Site Bleeding

Vascular access site bleeding is the most common type of bleeding after STEMI, particularly after PCI. PCI trials have identified female sex, advanced age, renal insufficiency, anemia, IABP, use of GP IIb/IIIa antagonists, and low-molecular-weight heparin within 48 hours of PCI as risk factors for femoral access site bleeding.[557] Larger sheath size, postprocedural heparin use, higher activated clotting times, and late postprocedural sheath removal increases the risk of access site bleeding and should be avoided. Radial artery access may decrease bleeding complications and should be considered whenever feasible,[558] but procedural success with this technique is dependent on operator experience.[559,560] Among patients with STEMI in the RIVAL (Radial Versus Femoral Access for Coronary Angiography and Intervention in Patients with Acute Coronary Syndromes) trial, radial artery access appeared to reduce the rate of the primary composite outcome (death, MI, stroke, non–CABG-related

major bleeding) and the individual secondary outcomes of death, MI, stroke, and overall mortality. However, rates of major bleeding were not lower with radial versus femoral access in patients with STEMI, though rates of major vascular complications were significantly reduced.[561] Although arterial closure devices have been associated with decreased femoral access site bleeding, more rapid hemostasis, and shorter duration of bed rest,[251,562,563] their routine use cannot be advocated specifically to reduce vascular complications after PCI, given the lack of robust, directionally consistent data on their efficacy and safety compared with manual compression.[564–566] Retroperitoneal bleeding should be suspected when the following are seen: unheralded intraprocedural or postprocedural hypotension and bradycardia (or tachycardia), high vascular puncture site, and an otherwise unexplained decrease in hemoglobin. Prompt computed tomographic imaging of the abdomen and pelvis may be helpful. Conservative management usually suffices, but early vascular interventional or surgical consultation should be obtained.[219]

9.8. Acute Kidney Injury

The risk of renal failure with STEMI relates to a host of factors, including patient age, prehospital renal function, medications, contrast volume, and hemodynamic status. Contrast-induced nephropathy after angiography and intervention for STEMI is always a risk, and attention to minimization of contrast volume and optimal hydration is required.[219]

9.9. Hyperglycemia

There is a U-shaped relationship between glucose levels and death in STEMI and ACS.[567] The mortality rate associated with hypoglycemia appears to be as high as the mortality rate associated with hyperglycemia.[568,569] Concern about overly aggressive glycemic control in critically ill patients was raised by the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial.[570] In this study of medical and surgical intensive care unit patients, tight glucose control (81 to 108 mg/dL) compared to modest control (<180 mg/dL) was associated with increased mortality rate (primarily from cardiovascular causes) and more episodes of hypoglycemia. Blood glucose levels should be maintained below 180 mg/dL if possible while avoiding hypoglycemia. There is no established role for glucose-insulin-potassium infusions in patients with STEMI.[571–573]

10. Risk Assessment After STEMI

Initial risk stratification should be performed early (Section 3) with the use of information available at the time of presentation. However, risk assessment is a continuous process that requires recalibration on the basis of data obtained during the hospital stay. Such data include the success of reperfusion therapy, events that occur during the hospital course (such as hemorrhagic complications), and the findings from noninvasive and invasive testing, particularly as they relate to the assessment of LV systolic function. For example, in patients treated with fibrinolytic therapy, clinical and ECG indicators of failed reperfusion identify individuals who should undergo urgent coronary angiography with intent to perform PCI.[356] In addition, the emergence of HF or significant LV systolic dysfunction is among the strongest predictors of higher-mortality risk after STEMI.

Stable patients with a low risk of complications may be candidates for early discharge. Among patients with STEMI managed with fibrinolysis, it has been suggested that an uncomplicated course after 72 hours of hospitalization identifies a group with sufficiently low risk to enable discharge.[574,575] Newby and colleagues calculated that extending the hospital stay of these patients by another day would cost $105 629 per year of life saved. However, the duration of hospitalization in patients treated with reperfusion therapy may be determined by other needs, such as patient education or titration of medications to optimum doses.[576]

Physicians and patients must individualize strategies for risk reduction, using lifestyle interventions, disease-modifying pharmacological therapies, and additional coronary revascularization when indicated. All patients with STEMI are considered to be at sufficiently high risk to merit interventions for secondary prevention, including the use of cardiac rehabilitation, aspirin, lipid-lowering therapy, beta blockers, and ACE inhibitors when indicated.[257] Additional risk assessment should be used to guide decisions about performance of coronary angiography in patients who did not undergo an invasive evaluation as part of their initial treatment strategy and to guide consideration of interventions to reduce the risk of SCD due to arrhythmia.

10.1. Use of Noninvasive Testing for Ischemia Before Discharge: Recommendations

Class I

1. **Noninvasive testing for ischemia should be performed before discharge to assess the presence and extent of inducible ischemia in patients with STEMI who have not had coronary angiography and do not have high-risk clinical features for which coronary angiography would be warranted.[577–579] (*Level of Evidence: B*)**

Class IIb

1. **Noninvasive testing for ischemia might be considered before discharge to evaluate the functional significance of a noninfarct artery stenosis previously identified at angiography. (*Level of Evidence: C*)**
2. **Noninvasive testing for ischemia might be considered before discharge to guide the postdischarge exercise prescription. (*Level of Evidence: C*)**

Noninvasive testing for ischemia provides valuable information about the presence of residual ischemia in patients who have not undergone cardiac catheterization during initial management of STEMI and may be useful in assessing the functional significance of a noninfarct artery stenosis identified at angiography. In the latter instance, stress imaging to localize ischemia would be appropriate.[580,581] Exercise testing early after STEMI may also be performed to 1) assess

functional capacity and the ability to perform tasks at home and at work, 2) evaluate the efficacy of medical therapy, and 3) assess the risk of a subsequent cardiac event. Symptom-limited exercise testing is a key feature of the intake evaluation for enrollment in a program of cardiac rehabilitation ≥2 weeks after discharge.[582]

Low-level exercise testing after MI appears to be safe if patients have undergone in-hospital cardiac rehabilitation, including low-level exercise; have had no symptoms of angina or HF; and have a stable baseline ECG 48 to 72 hours before the test.[583] Two different protocols have been used for early post-MI exercise testing: the traditional submaximal exercise test (done at 3 to 5 days in patients without complications) or a symptom-limited exercise test (done at 5 days or later) without stopping at a prespecified target heart rate or metabolic equivalent level. RCTs of early exercise testing after PCI have excluded patients with recent MI.[584] Limited data exist on the safety of early symptom-limited exercise testing after MI; therefore, clinical judgment must be used.[585] Pharmacological stress myocardial perfusion imaging has been shown to have predictive value for postinfarction cardiac events and is useful and safe in patients who are unable to exercise.[586] The optimum timing for provocative testing for ischemia after STEMI remains unresolved. It is argued that a predischarge exercise test may provide psychological benefit to the patient and will permit detection of profound ischemia or other indicators of high risk that could be associated with postdischarge cardiac events that might occur before a symptom-limited stress test scheduled weeks later.[585] A predischarge study also provides parameters for exercise prescription in the first few days after return home, before enrollment in cardiac rehabilitation. 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 the writing committee that patients without complications *who have not undergone coronary angiography* and who might be potential candidates for revascularization should undergo provocative testing before hospital discharge. In patients with noninfarct artery disease who have undergone successful PCI of the infarct artery and have an uncomplicated course, it is reasonable to proceed with discharge and plans for close clinical follow-up with stress imaging within 3 to 6 weeks.

10.2. Assessment of LV Function: Recommendation

Class I

1. **LVEF should be measured in all patients with STEMI. (*Level of Evidence: C*)**

LV function is one of the strongest predictors of survival in patients with STEMI. LV function most commonly is evaluated with contrast ventriculography at the time of cardiac catheterization or with transthoracic echocardiography on day 2 or 3. Echocardiography is the most frequently used imaging modality to evaluate regional and global LV function after STEMI and can help characterize any associated mechanical complications when they are clinically suspected. Because of the dynamic nature of LV functional recovery after STEMI, clinicians should consider the timing of the imaging study relative to the index event. In patients with significant LV systolic dysfunction revealed during the initial hospitalization, LV function should be reevaluated ≥40 days later, especially to address the potential need for ICD therapy after allowance for recovery from myocardial stunning.[496,587,588]

10.3. Assessment of Risk for SCD: Recommendation

Class I

1. **Patients with an initially reduced LVEF who are possible candidates for ICD therapy should undergo reevaluation of LVEF 40 or more days after discharge.[496,587–589] (*Level of Evidence: B*)**

The timing and character of ventricular arrhythmias and residual LV systolic function are the strongest predictors of SCD risk after STEMI. Management considerations for patients with ventricular arrhythmias during the hospital phase are reviewed in Section 9.5. Hospital survivors with an initially reduced LVEF (≤0.40) who do not merit ICD therapy before discharge should undergo reassessment of LV function ≥40 days later to determine their eligibility for ICD therapy. The recommended delay to ICD therapy in this setting stems from the results of DINAMIT (Defibrillator in Acute Myocardial Infarction Trial), in which defibrillator implantation 6 to 40 days after MI in patients with EF ≤0.35 and impaired cardiac autonomic function was not shown to reduce overall cardiac death risk. The observed reduction in arrhythmic deaths was offset by a relative increase in the numbers of nonarrhythmic deaths.[587] The IRIS (Immediate Risk Stratification Improves Survival) trial[588] also showed that early ICD therapy in patients with LVEF ≤0.40 and a high heart rate, nonsustained VT regardless of LVEF, or both did not result in improved survival. The utility of a wearable cardioverter-defibrillator in high-risk patients during the first 4 to 6 weeks after STEMI is under investigation http://clinicaltrials.gov/ct2/show/NCT00628966).

The indications for ICD therapy ≥40 days after STEMI are based on LVEF and New York Heart Association class, as derived from the results of the landmark MADIT 2 (Multicenter Automatic Defibrillator Implantation Trial 2) and SCDHeFT (Sudden Cardiac Death in Heart Failure) trials.[496,589–591] If LVEF remains ≤0.35 and the patient has New York Heart Association class II or III HF symptoms, or if the LVEF is ≤0.30 independent of symptoms, then ICD implantation is recommended.[496] Indications for cardiac resynchronization therapy in the late, convalescent phase of STEMI include residual LV function, New York Heart Association class, QRS duration, and LBBB morphology.[592]

In addition to determination of LVEF, several other noninvasive strategies have been proposed to identify patients at high risk for arrhythmic events after STEMI, such as signal-averaged or high-resolution ECG, heart rate variability, baroreflex sensitivity, and T-wave alternans.[591] These strategies have not been adopted widely because of their limited

performance characteristics and are not recommended for routine use.

11. Posthospitalization Plan of Care

11.1. Posthospitalization Plan of Care: Recommendations

Class I

1. **Posthospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care for all patients with STEMI.[593–597] (*Level of Evidence: B*)**
2. **Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI.[598–601] (*Level of Evidence: B*)**
3. **A clear, detailed, and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI. (*Level of Evidence: C*)**
4. **Encouragement and advice to stop smoking and to avoid secondhand smoke should be provided to patients with STEMI.[602–605] (*Level of Evidence: A*)**

11.1.1. The Plan of Care for Patients With STEMI

Education of patients with STEMI and their families is critical and often challenging, especially when transitions of care occur. Failure to understand and comply with a plan of care may account for the high rate of STEMI rehospitalization rates seen in the United States.[19,606] One key intervention to ensure effective coordination is to provide to patients and caregivers, during the hospital stay, a comprehensive plan of care and educational materials that promote compliance with recommended evidence-based therapies.[607–609] The posthospitalization plan of care for patients with STEMI should address in detail several complex issues, including medication adherence and titration, timely follow-up, dietary interventions, physical and sexual activities, cardiac rehabilitation, compliance with interventions for secondary prevention (Table 14), and reassessment of arrhythmic and HF risks. In addition, providers should pay close attention to psychosocial and socioeconomic issues, including access to care, risk of depression, social isolation, and healthcare disparities.[610–612]

11.1.2. Smoking Cessation

The value of smoking cessation for the secondary prevention of cardiovascular disease has been demonstrated in several prospective observational studies. A meta-analysis of cohort studies in patients after acute MI showed that smoking cessation reduced the subsequent cardiovascular mortality rate by nearly 50%,[602] ranking it among the most powerful secondary prevention strategies.[603] The SAVE (Sleep Apnea Cardiovascular Endpoints) study investigators reported that in selected patients with LV systolic dysfunction after MI, smoking cessation, compared with continued smoking, is associated with a 40% lower hazard of all-cause mortality and a 30% lower hazard of death, recurrent MI, or HF hospitalization.[605]

Reasonable evidence from RCTs indicates that counseling hospitalized smokers after acute MI increases smoking cessation rates, provided that the initial contact during the hospital stay is followed by repeated contacts, usually by telephone, for ≥3 months after discharge.[603,604] Similarly, the odds of smoking cessation are greater among patients who receive discharge recommendations for cardiac rehabilitation.[604] Patients with depressive symptoms during the MI hospitalization and early convalescence are less likely to quit smoking and may require more intensive treatment to achieve cessation.[603,604] Counseling should be provided to the patient and family, along with pharmacological therapy as deemed safe, and access to formal smoking-cessation programs should be facilitated.

11.1.3. Cardiac Rehabilitation

The objectives of contemporary exercise-based cardiac rehabilitation are to increase functional capacity, decrease or alleviate anginal symptoms, reduce disability, improve quality of life, modify coronary risk factors, and reduce morbidity and mortality rates.[598,613,614] Core components include patient assessment; ongoing medical surveillance; nutritional counseling; BP, lipid, and diabetes mellitus management; smoking cessation; psychosocial counseling; physical activity counseling; exercise training; and pharmacological treatment, as appropriate.[614]

Among 601 099 US Medicare beneficiaries who were hospitalized for coronary conditions or revascularization procedures, mortality rates were 21% to 34% lower among participants in cardiac rehabilitation programs than among nonparticipants.[599] It has been suggested that contemporary reperfusion and cardioprotective drug therapies may diminish the impact of adjunctive exercise-based cardiac rehabilitation programs on post-MI survival rate. Taylor et al[600] conducted a systematic review and meta-analysis of RCTs of cardiac rehabilitation with ≥6 months of follow-up. The study population included 8940 patients, a greater number were women (20% of the cohort), patients ≥65 years of age, and individuals who had undergone revascularization procedures. Compared with usual care, cardiac rehabilitation was associated with a reduction in total and cardiac mortality rates of 20% and 26%, respectively. Subgroup analyses showed that the decreased mortality rates did not differ across several patient subsets, between programs limited to exercise and those providing more comprehensive secondary interventions, or between pre- and post-1995 studies, which suggests that the mortality benefits of cardiac rehabilitation persist in the modern era. However, despite these impressive outcomes, cardiac rehabilitation services remain vastly underutilized.[582,615]

11.1.4. Systems of Care to Promote Care Coordination

Meaningful evidence has facilitated a much better understanding of the systems changes necessary to achieve safer care.[616] This includes the adoption by all US hospitals of a standardized set of "Safe Practices" endorsed by the National Quality Forum,[617] which overlap in many ways with the National Patient Safety Goals espoused by The Joint Commission.[618] Examples of patient safety standards that should be ensured for all patients discharged after STEMI include

Table 14. Plan of Care for Patients With STEMI

Plan of Care	Resources/References
Medications	
• Antithrombotic therapies	Sections 4.4, 5.1, 6.4
• Beta blockers	Section 8.1
• ACE inhibitors/ARBs/aldosterone antagonists	Section 8.2
• Statins	Section 8.3
	ESC STEMI Guideline[48]
	ACC/AHA 2012 SIHD Guideline[614]
Physical activity/cardiac rehabilitation	
• Physical activity	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
• Cardiorespiratory fitness (MET capacity)	AACVPR/ACCF/AHA 2010 Update: Performance Measures on Cardiac Rehabilitation[616]
Risk factor modification/lifestyle interventions	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
• Smoking cessation	ACCP Tobacco Cessation Toolkit[615]
• Diet/nutrition	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
Management of comorbidities	
• Overweight/obesity	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
• Lipids	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
• Hypertension	NHLBI National Hypertension Education Program (JNC VII)[617]
• Diabetes	AHA/ADA CVD Prevention in DM Patients[618]
• HF	ACC/AHA/HFSA HF Guideline[619]
• Arrhythmia/arrhythmia risk	ACC/AHA/HRS DBT & AF Guidelines[496,501]
Psychosocial factors	
• Sexual activity	AHA Scientific Statement on Sexual Activity and Cardiovascular Disease[627a]
• Gender-specific issues	Cardiovascular Disease Prevention in Women Guidelines[620]
• Depression, stress, and anxiety	AHA Scientific Statement on Depression[621]
• Alcohol use	AHA/ACC 2011 Update: Secondary Prevention and Risk Reduction Therapy[249]
• Culturally sensitive issues	
Provider follow-up	
• Cardiologist	H2H Quality Initiative http://www.h2hquality.org
• Primary care provider	
• Advanced practice nurse/physician assistant	
• Other relevant medical specialists	
• Electronic personal health records	
• Influenza vaccination	Centers for Disease Control Adult Vaccinations[622]
Patient/family education	
• Plan of care for acute MI	AHA CPR Guideline[201]
• Recognizing symptoms of MI	
• Activating EMS, signs and symptoms for urgent vs emergency evaluations	
• CPR training for family members	
• Risk assessment & prognosis	
• Advanced directives	
• Social networks/social isolation	
Socioeconomic factors	
• Access to health insurance coverage	http://www.qualityforum.org/Topics/Care_Coordination.Aspx
• Access to healthcare providers	
• Disability	
• Social services	
• Community services	

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; CPR, cardiopulmonary resuscitation; CVD, cardiovascular disease; DBT, device-based therapy; DM, diabetes mellitus; EMS, emergency medical services; ESC, European Society of Cardiology; H2H, hospital-to-home; HF, heart failure; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; JNC, Joint National Committee; MET, metabolic equivalent; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; SIHD, stable ischemic heart disease; and STEMI, ST-elevation myocardial infarction.

improved communication among physicians, nurses, and pharmacists; medication reconciliation; careful transitions between care settings; and consistent documentation. The National Quality Forum also has endorsed a set of patient-centered "Preferred Practices for Care Coordination,"[619] which detail comprehensive specifications that are necessary to achieve the goals of successful care coordination for patients and their families. Systems of care designed to support patients with STEMI and other cardiac diseases can result in significant improvement in patient outcomes. To provide the interventions and services listed in Table 14, appropriate resources must be applied to ensure that all patients with STEMI have full access to evidence-based therapies and follow-up care. There is a growing emphasis on penalizing hospitals for avoidable hospital readmissions. Hence, it is imperative for health systems to work in partnership with physicians, nurses, pharmacists, communities, payers, and public agencies to support the interventions that achieve such comprehensive care.

Patient characteristics may be important predictors of readmission after MI; however, only a few variables have been identified consistently.[620,621] From a policy perspective, a validated risk-standardized model that uses readmission rates to profile hospitals is not currently available.

12. Unresolved Issues and Future Research Directions

The writing committee has identified several areas pertaining to the management of patients with STEMI that deserve further research. Although the observations from the Swedish STEMI registry showing an association between the increased use of evidence-based treatments and declining mortality rates after STEMI are encouraging,[18] additional efforts to improve patient outcomes are needed. There is widespread acknowledgment that progress in closing existing knowledge and performance gaps will require contributions from a wide range of investigators, dedicated clinicians, hospital and health plan administrators, regional emergency response systems, and both government and private payers.[631]

12.1. Patient Awareness

Delay times from onset of symptoms to activation of STEMI care pathways remain unacceptably long.[51,631] Multicultural efforts to educate, reassure, and motivate at-risk patients and their families are needed. Comparable efforts to improve adherence and attention to healthy lifestyle behaviors as the cornerstones of secondary prevention are required at time of discharge and as an integral feature of cardiac rehabilitation programs.

12.2. Regional Systems of Care

The adoption of regional systems of care for patients with STEMI across diverse geographical areas has proved challenging, and inappropriate delays to initiation of reperfusion therapy are common.[632] As previously emphasized, attention should be focused on *reducing the total ischemic time*, from onset of symptoms to successful reperfusion. Several factors in addition to patient activation of EMS contribute to delays, not all of which can be reconciled. Areas for continued research include prehospital EMS protocols, the approach to out-of-hospital cardiac arrest, triage and transfer algorithms, rapid availability of expert PCI services, and further refinement of the clinical and time-related factors that should prompt earlier use of fibrinolytic therapy coupled with immediate transfer for PCI.[129,633–635] The lack of correlation between shorter D2B times and reduced mortality should drive further efforts to improve all aspects of STEMI care.[636] Regional systems should track, analyze, and report all STEMI and out-of-hospital cardiac arrest events as part of an ongoing process-improvement program.

12.3. Transfer and Management of Non–High-Risk Patients After Administration of Fibrinolytic Therapy

The indications for and timing of transfer for angiography with a view toward revascularization of *non–high-risk patients* after successful fibrinolysis are still debated. Although there has been increasing activation of this pathway, the evidence base for its justification is still limited.[358,360,365]

12.4. Antithrombotic Therapy

The optimum choice of $P2Y_{12}$ receptor inhibitor and anticoagulant agents for patients with STEMI can be challenging. Individual genetic variability in drug absorption, metabolism, and effectiveness has been highlighted by the experience with clopidogrel in patients with ACS.[285,637] The risks of bleeding also may vary across racial and ethnic groups.[12] The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain,[289] especially with the availability of alternative $P2Y_{12}$ receptor inhibitors. More information specific to patients with STEMI is needed with regard to the use of prasugrel, ticagrelor, novel factor Xa and IIa antagonists, and platelet protease–activated receptor 1 antagonists.[638,639] The efficacy and safety of combination ("triple") antithrombotic therapy must be addressed continuously,[525,537] while less hazardous approaches are tested. Bleeding rates with radial versus femoral artery access for PCI warrant further prospective study.[561]

12.5. Reperfusion Injury

Aside from manual aspiration thrombectomy, efforts to counteract the "no-reflow" phenomenon and to limit myocardial reperfusion injury have had limited success. The value of aspiration thrombectomy in patients with anterior STEMI has been questioned.[223] Remote ischemic preconditioning has engendered little enthusiasm. Trials evaluating the use of antithrombotic and vasodilator agents have been disappointing. New biological, pharmacological, and mechanical strategies should be investigated to facilitate prompt recovery of tissue-level perfusion.[220,640–642,644] In addition, high-dose statin pretreatment before primary or delayed PCI for STEMI requires further study.[645]

12.6. Approach to Noninfarct Artery Disease

There is great variability in the evaluation and management of nonculprit coronary artery disease in stable patients without HF or shock, both at the time of primary PCI and later during the hospital course. Physiological assessment of lesion significance is often not performed, and the decision to proceed with PCI is made on anatomic grounds. More work is needed to clarify the indications for and timing of noninfarct artery revascularization.[218,224,228,229]

12.7. Prevention of SCD

Prediction of electrical vulnerability and SCD risk after STEMI is fraught with imprecision. Treatment decisions rely almost exclusively on parameters of LV systolic function. Optimal therapy for at-risk individuals in the time window between discharge and 40 days, the time point after which ICD therapy is currently recommended, has not been established. Improved prediction rules and validated treatment recommendations are urgently needed.[646]

12.8. Prevention of HF

Much progress has been made to limit LV remodeling, though there remains substantial room for improvement, beginning with the timeliness of reperfusion and initiation of ACE inhibitor/ARB therapy.[627] The superimposition of ischemic mitral regurgitation adds further to the risks of HF and death. Continued exploration of the roles of cell- and gene-based therapies after STEMI is encouraged.[647–656]

Presidents and Staff

References

1. ACCF/AHA Task Force on Practice Guidelines. Manual for ACCF/AHA Guideline Writing Committees: Methodologies and Policies from the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2006. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf and http://my.americanheart.org/professional/StatementsGuidelines/PoliciesDevelopment/Development/Methodologies-and-Policies-from-the-ACCAHA-Task-Force-on-Practice-Guidelines_UCM_320470_Article.jsp. Accessed July 26, 2012.
2. Eden J, Levit L, Berg A, et al, eds; Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011.
3. Graham R, Mancher M, Miller Wolman D, et al, editors; Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press; 2011.
4. Antman EM, Anbe DT, Armstrong PW, et al. 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). Circulation. 2004;110:e82–292.
5. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused update of the ACC/AHA 2004 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. Circulation. 2008;117:296–329.
6. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120:2271–2306. Erratum in: Circulation. 2010;121:e257.
7. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126:2020–35.
8. Jain S, Ting HT, Bell M, et al. Utility of left bundle branch block as a diagnostic criterion for acute myocardial infarction. Am J Cardiol. 2011; 107:1111–6.
9. Go AS, Barron HV, Rundle AC, et al; for the National Registry of Myocardial Infarction 2 Investigators. Bundle-branch block and in-hospital mortality in acute myocardial infarction. Ann Intern Med. 1998;129:690–7.
10. de Winter RJ, Verouden NJW, Wellens HJJ, et al. A new ECG sign of proximal LAD occlusion. N Engl J Med. 2008;359:2071–3.
11. Jong G-P, Ma T, Chou P, et al. Reciprocal changes in 12-lead electrocardiography can predict left main coronary artery lesion in patients with acute myocardial infarction. Int Heart J. 2006;47:13–20.
12. Mehta RH, Parsons L, Rao SV, et al. Association of bleeding and in-hospital mortality in black and white patients with ST-segment-elevation myocardial infarction receiving reperfusion. Circulation. 2012;125:1727–34.
13. Fox KAA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. JAMA. 2007;297: 1892–900.
14. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155–65.
15. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006;27:2285–93.
16. McManus DD, Gore J, Yarzebski J, et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med. 2011;124:40–7.
17. Roe MT, Messenger JC, Weintraub WS, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. J Am Coll Cardiol. 2010;56:254–63.
18. Jernberg T, Johanson P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA. 2011;305:1677–84.
19. Krumholz HM, Merrill AR, Schone EM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes. 2009;2:407–13.
20. Bradley EH, Curry LA, Spatz ES, et al. Hospital strategies for reducing risk-standardized mortality rates in acute myocardial infarction. Ann Intern Med. 2012;156:618–26.
21. Gharacholou SM, Alexander KP, Chen AY, et al. Implications and reasons for the lack of use of reperfusion therapy in patients with ST-segment elevation myocardial infarction: findings from the CRUSADE initiative. Am Heart J. 2010;159:757–63.
22. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation. 2009;119:1873–82.

23. Glickman SW, Granger CB, Ou F-S, et al. Impact of a statewide ST-segment-elevation myocardial infarction regionalization program on treatment times for women, minorities, and the elderly. Circ Cardiovasc Qual Outcomes. 2010;3:514–21.
24. Wynia MK, Ivey SL, Hasnain-Wynia R. Collection of data on patients' race and ethnic group by physician practices. N Engl J Med. 2010;362:846–50.
25. Grundy SM, Garber A, Goldberg R, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group IV: lifestyle and medical management of risk factors. Circulation. 2002;105:e153–8.
26. Eckel RH, Kahn R, Robertson RM, et al. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation. 2006;113:2943–6.
27. Rasoul S, Ottervanger JP, de Boer M-J, et al. Predictors of 30-day and 1-year mortality after primary percutaneous coronary intervention for ST-elevation myocardial infarction. Coron Artery Dis. 2009;20:415–21.
28. De Luca G, Gibson CM, Bellandi F, et al. Diabetes mellitus is associated with distal embolization, impaired myocardial perfusion, and higher mortality in patients with ST-segment elevation myocardial infarction treated with primary angioplasty and glycoprotein IIb-IIIa inhibitors. Atherosclerosis. 2009;207:181–5.
29. Svensson A-M, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J. 2005;26:1255–61.
30. Worthley MI, Shrive FM, Anderson TJ, et al. Prognostic implication of hyperglycemia in myocardial infarction and primary angioplasty. Am J Med. 2007;120:643–7.e1–7.
31. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355:773–8.
32. Timmer JR, van der Horst ICC, Ottervanger JP, et al. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. Am Heart J. 2004;148:399–404.
33. Ishihara M, Kagawa E, Inoue I, et al. Impact of admission hyperglycemia and diabetes mellitus on short- and long-term mortality after acute myocardial infarction in the coronary intervention era. Am J Cardiol. 2007;99:1674–9.
34. Porter A, Assali AR, Zahalka A, et al. Impaired fasting glucose and outcomes of ST-elevation acute coronary syndrome treated with primary percutaneous intervention among patients without previously known diabetes mellitus. Am Heart J. 2008;155:284–9.
35. Marso SP, Miller T, Rutherford BD, et al. Comparison of myocardial reperfusion in patients undergoing percutaneous coronary intervention in ST-segment elevation acute myocardial infarction with versus without diabetes mellitus (from the EMERALD Trial). Am J Cardiol. 2007;100:206–10.
36. Timmer JR, van der Horst ICC, de Luca G, et al. Comparison of myocardial perfusion after successful primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction with versus without diabetes mellitus. Am J Cardiol. 2005;95:1375–7.
37. Alexander KP, Newby LK, Armstrong PW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115:2570–89.
38. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115:2549–69.
39. Michaels AD, Spinler SA, Leeper B, et al. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. Circulation. 2010;121:1664–82.
40. Shah P, Najafi AH, Panza JA, et al. Outcomes and quality of life in patients > or =85 years of age with ST-elevation myocardial infarction. Am J Cardiol. 2009;103:170–4.
41. Lewis WR, Ellrodt AG, Peterson E, et al. Trends in the use of evidence-based treatments for coronary artery disease among women and the elderly: findings from the Get With The Guidelines Quality-Improvement Program. Circ Cardiovasc Qual Outcomes. 2009;2:633–41.
42. Herzog CA. Acute myocardial infarction in patients with end-stage renal disease. Kidney Int Suppl. 1999;71:S130–3.
43. Reddan DN, Szczech L, Bhapkar MV, et al. Renal function, concomitant medication use and outcomes following acute coronary syndromes. Nephrol Dial Transplant. 2005;20:2105–12.
44. Shlipak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med. 2002;137:555–62.
45. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol. 2003;42:201–8.
46. Medi C, Montalescot G, Budaj A, et al. Reperfusion in patients with renal dysfunction after presentation with ST-segment elevation or left bundle branch block: GRACE (Global Registry of Acute Coronary Events). JACC Cardiovasc Interv. 2009;2:26–33.
47. Tsai TT, Maddox TM, Roe MT, et al. Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. JAMA. 2009;302:2458–64.
48. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008;29:2909–45.
49. Mehta RH, Califf RM, Garg J, et al. The impact of anthropomorphic indices on clinical outcomes in patients with acute ST-elevation myocardial infarction. Eur Heart J. 2007;28:415–24.
50. Goldberg RJ, Spencer FA, Fox KAA, et al. Prehospital delay in patients with acute coronary syndromes (from the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol. 2009;103:598–603.
51. Spencer FA, Montalescot G, Fox KAA, et al. Delay to reperfusion in patients with acute myocardial infarction presenting to acute care hospitals: an international perspective. Eur Heart J. 2010;31:1328–36.
52. Goff DC Jr, Feldman HA, McGovern PG, et al; Rapid Early Action for Coronary Treatment (REACT) Study Group. Prehospital delay in patients hospitalized with heart attack symptoms in the United States: the REACT trial. Am Heart J. 1999;138:1046–57.
53. Goldberg RJ, Steg PG, Sadiq I, et al. Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (the GRACE registry). Am J Cardiol. 2002;89:791–6.
54. Finnegan JR Jr, Meischke H, Zapka JG, et al. Patient delay in seeking care for heart attack symptoms: findings from focus groups conducted in five U.S. regions. Prev Med. 2000;31:205–13.
55. McKinley S, Moser DK, Dracup K. Treatment-seeking behavior for acute myocardial infarction symptoms in North America and Australia. Heart Lung. 2000;29:237–47.
56. Feldman HA, Proschan MA, Murray DM, et al. Statistical design of REACT (Rapid Early Action for Coronary Treatment), a multisite community trial with continual data collection. Control Clin Trials. 1998;19:391–403.
57. Leslie WS, Urie A, Hooper J, et al. Delay in calling for help during myocardial infarction: reasons for the delay and subsequent pattern of accessing care. Heart. 2000;84:137–41.
58. Rucker D, Brennan T, Burstin H. Delay in seeking emergency care. Acad Emerg Med. 2001;8:163–9.
59. Wenger NK. You've come a long way, baby: cardiovascular health and disease in women: problems and prospects. Circulation. 2004;109:558–60.
60. Dracup K, Alonzo AA, Atkins JM, et al; Working Group on Educational Strategies to Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction. The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: recommendations from the National Heart Attack Alert Program. Ann Intern Med. 1997;126:645–51.
61. Alonzo AA. The impact of the family and lay others on care-seeking during life-threatening episodes of suspected coronary artery disease. Soc Sci Med. 1986;22:1297–311.
62. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) Trial. JAMA. 2000;284:60–7.
63. National Emergency Number Association. Available at: http://www.nena.org. Accessed July 26, 2012.

64. Mathews R, Peterson ED, Li S, et al. Use of emergency medical service transport among patients with ST-segment-elevation myocardial infarction: findings from the National Cardiovascular Data Registry Acute Coronary Treatment Intervention Outcomes Network Registry-Get With The Guidelines. Circulation. 2011;124:154–63.
65. Brown AL, Mann NC, Daya M, et al. Demographic, belief, and situational factors influencing the decision to utilize emergency medical services among chest pain patients: Rapid Early Action for Coronary Treatment (REACT) study. Circulation. 2000;102:173–8.
66. Canto JG, Zalenski RJ, Ornato JP, et al. Use of emergency medical services in acute myocardial infarction and subsequent quality of care: observations from the National Registry of Myocardial Infarction 2. Circulation. 2002;106:3018–23.
67. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. Ann Emerg Med. 1996;28:612–6.
68. Hutchings CB, Mann NC, Daya M, et al. Patients with chest pain calling 9-1-1 or self-transporting to reach definitive care: which mode is quicker? Am Heart J. 2004;147:35–41.
69. Ting HH, Krumholz HM, Bradley EH, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008;118:1066–79.
70. Sørensen JT, Terkelsen CJ, Nørgaard BL, et al. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. Eur Heart J. 2011;32:430–6.
71. Le May MR, So DY, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008;358:231–40.
72. Rokos IC, French WJ, Koenig WJ, et al. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. JACC Cardiovasc Interv. 2009;2:339–46.
73. Faxon D, Lenfant C. Timing is everything: motivating patients to call 9-1-1 at onset of acute myocardial infarction. Circulation. 2001;104:1210–1.
74. National Institutes of Health, US Department of Health and Human Services. Act in Time. National Heart, Lung, and Blood Institute. Available at: http://health.nih.gov/topic/HeartAttack/. Accessed July 26, 2012.
75. McDermott MM, Mandapat AL, Moates A, et al. Knowledge and attitudes regarding cardiovascular disease risk and prevention in patients with coronary or peripheral arterial disease. Arch Intern Med. 2003;163:2157–62.
76. Aguirre FV, Varghese JJ, Kelley MP, et al. Rural interhospital transfer of ST-elevation myocardial infarction patients for percutaneous coronary revascularization: the Stat Heart Program. Circulation. 2008;117:1145–52.
77. Henry TD, Sharkey SW, Burke MN, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation. 2007;116:721–8.
78. Jollis JG, Roettig ML, Aluko AO, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. JAMA. 2007;298:2371–80.
79. Dieker H-J, Liem SSB, El Aidi H, et al. Pre-hospital triage for primary angioplasty: direct referral to the intervention center versus interhospital transport. JACC Cardiovasc Interv. 2010;3:705–11.
80. Diercks DB, Kontos MC, Chen AY, et al. Utilization and impact of prehospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. J Am Coll Cardiol. 2009;53:161–6.
81. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet. 1994;343:311–22. Erratum in: Lancet. 1994;343:742.
82. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.
83. Andersen HR, Nielsen TT, Vesterlund T, et al. Danish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction: rationale and design of the DANish trial in Acute Myocardial Infarction-2 (DANAMI-2). Am Heart J. 2003;146: 234–41.
84. Dalby M, Bouzamondo A, Lechat P, et al. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation. 2003;108:1809–14.
85. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med. 2003;349:733–42.
86. Nielsen PH, Terkelsen CJ, Nielsen TT, et al. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). Am J Cardiol. 2011;108:776–81.
87. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? Am J Cardiol. 2003;92:824–6.
88. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation. 2006;114:2019–25.
89. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996; 348:771–5.
90. Chareonthaitawee P, Gibbons RJ, Roberts RS, et al; for the CORE investigators (Collaborative Organisation for RheothRx Evaluation). The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. Heart. 2000;84:142–8.
91. McNamara RL, Herrin J, Wang Y, et al. Impact of delay in door-to-needle time on mortality in patients with ST-segment elevation myocardial infarction. Am J Cardiol. 2007;100:1227–32.
92. Milavetz JJ, Giebel DW, Christian TF, et al. Time to therapy and salvage in myocardial infarction. J Am Coll Cardiol. 1998;31:1246–51.
93. Newby LK, Rutsch WR, Califf RM, et al; GUSTO-1 Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol. 1996;27:1646–55.
94. Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. JAMA. 2005;293:2865–72.
95. Gierlotka M, Gasior M, Wilczek K, et al. Reperfusion by primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction within 12 to 24 hours of the onset of symptoms (from a prospective national observational study [PL-ACS]). Am J Cardiol. 2011;107:501–8.
96. Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ. 2009;338:b1807.
97. Terkelsen CJ, Jensen LO, Tilsted H-H, et al. Health care system delay and heart failure in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: follow-up of population-based medical registry data. Ann Intern Med. 2011;155:361–7.
98. De Luca G, Suryapranata H, Ottervanger JP, et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109:1223–5.
99. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304:763–71.
100. Pinto DS, Frederick PD, Chakrabarti AK, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124:2512–21.
101. Armstrong PW, Boden WE. Reperfusion paradox in ST-segment elevation myocardial infarction. Ann Intern Med. 2011;155:389–91.
102. Bates ER, Nallamothu BK. Commentary: the role of percutaneous coronary intervention in ST-segment-elevation myocardial infarction. Circulation. 2008;118:567–73.
103. Ellis SG, Armstrong P, Betriu A, et al. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. Am Heart J. 2004;147:E16.

104. Krumholz HM, Bradley EH, Nallamothu BK, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: An Alliance for Quality. JACC Cardiovasc Interv. 2008;1:97–104.
105. Bradley EH, Nallamothu BK, Stern AF, et al. The Door-to-Balloon Alliance for Quality: who joins national collaborative efforts and why? Jt Comm J Qual Patient Saf. 2009;35:93–9.
106. Jacobs AK, Antman EM, Faxon DP, et al. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. Circulation. 2007;116:217–30. Erratum in: Circulation. 2007;116:e77.
107. Antman EM. Time is muscle: translation into practice. J Am Coll Cardiol. 2008;52:1216–21.
108. Kontos MC, Kurz MC, Roberts CS, et al. An evaluation of the accuracy of emergency physician activation of the cardiac catheterization laboratory for patients with suspected ST-segment elevation myocardial infarction. Ann Emerg Med. 2010;55:423–30.
109. Lee CH, Van Gelder CM, Cone DC. Early cardiac catheterization laboratory activation by paramedics for patients with ST-segment elevation myocardial infarction on prehospital 12-lead electrocardiograms. Prehosp Emerg Care. 2010;14:153–8.
110. Trivedi K, Schuur JD, Cone DC. Can paramedics read ST-segment elevation myocardial infarction on prehospital 12-lead electrocardiograms? Prehosp Emerg Care. 2009;13:207–14.
111. Willson AB, Mountain D, Jeffers JM, et al. Door-to-balloon times are reduced in ST-elevation myocardial infarction by emergency physician activation of the cardiac catheterisation laboratory and immediate patient transfer. Med J Aust. 2010;193:207–12.
112. Youngquist ST, Shah AP, Niemann JT, et al. A comparison of door-to-balloon times and false-positive activations between emergency department and out-of-hospital activation of the coronary catheterization team. Acad Emerg Med. 2008;15:784–7.
113. Larson DM, Menssen KM, Sharkey SW, et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. JAMA. 2007;298:2754–60.
114. Garvey JL, Monk L, Granger CB, et al. Rates of cardiac catheterization cancelation for ST-segment elevation myocardial infarction after activation by emergency medical services or emergency physicians: results from the North Carolina Catheterization Laboratory Activation Registry. Circulation. 2012;125:308–13.
115. Rokos IC, French WJ, Mattu A, et al. Appropriate cardiac cath lab activation: optimizing electrocardiogram interpretation and clinical decision-making for acute ST-elevation myocardial infarction. Am Heart J. 2010;160:995–1003, 1003.e1–8.
116. Mixon TA, Suhr E, Caldwell G, et al. Retrospective description and analysis of consecutive catheterization laboratory ST-segment elevation myocardial infarction activations with proposal, rationale, and use of a new classification scheme. Circ Cardiovasc Qual Outcomes. 2012;5:62–9.
117. Jacobs AK. Primary percutaneous coronary intervention without cardiac surgery on-site: coming to a hospital near you? Am Heart J. 2008;155:585–8.
118. Jollis JG, Mehta RH, Roettig ML, et al. Reperfusion of acute myocardial infarction in North Carolina emergency departments (RACE): study design. Am Heart J. 2006;152:851.e1–11.
119. Kalla K, Christ G, Karnik R, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation. 2006;113:2398–405.
120. Rokos IC, Larson DM, Henry TD, et al. Rationale for establishing regional ST-elevation myocardial infarction receiving center (SRC) networks. Am Heart J. 2006;152:661–7.
121. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. Circulation. 2007;116:729–36.
122. American Heart Association. Mission Lifeline. Available at: http://www.heart.org/HEARTORG/HealthcareResearch/MissionLifelineHomePage/Mission-Lifeline-Home-Page_UCM_305495_SubHomePage.jsp. Accessed July 26, 2012.
123. Bonnefoy E, Steg PG, Boutitie F, et al. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J. 2009;30:1598–606.
124. Bradley EH, Curry LA, Ramanadhan S, et al. Research in action: using positive deviance to improve quality of health care. Implement Sci. 2009;4:25.
125. Widimský P, Budesínský T, Vorác D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial: PRAGUE-2. Eur Heart J. 2003;24:94–104.
126. Chakrabarti A, Krumholz HM, Wang Y, et al. Time-to-reperfusion in patients undergoing interhospital transfer for primary percutaneous coronary intervention in the U.S: an analysis of 2005 and 2006 data from the National Cardiovascular Data Registry. J Am Coll Cardiol. 2008;51:2442–3.
127. Wang TY, Peterson ED, Ou F-S, et al. Door-to-balloon times for patients with ST-segment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. Am Heart J. 2011;161:76–83.e1.
128. Miedema MD, Newell MC, Duval S, et al. Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. Circulation. 2011;124:1636–44.
129. Wang TY, Nallamothu BK, Krumholz HM, et al. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. JAMA. 2011;305:2540–7.
130. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet. 2006;367:569–78.
131. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med. 2008;358:2205–17.
132. Bradley EH, Herrin J, Wang Y, et al. Door-to-drug and door-to-balloon times: where can we improve? Time to reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI). Am Heart J. 2006;151:1281–7.
133. Jacobs AK, Antman EM, Ellrodt G, et al. Recommendation to develop strategies to increase the number of ST-segment-elevation myocardial infarction patients with timely access to primary percutaneous coronary intervention. Circulation. 2006;113:2152–63.
134. McNamara RL, Herrin J, Bradley EH, et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. J Am Coll Cardiol. 2006;47:45–51.
135. Bradley EH, Curry LA, Webster TR, et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. Circulation. 2006;113:1079–85.
136. Bradley EH, Nallamothu BK, Herrin J, et al. National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance. J Am Coll Cardiol. 2009;54:2423–9.
137. Nestler DM, Noheria A, Haro LH, et al. Sustaining improvement in door-to-balloon time over 4 years: the Mayo Clinic ST-elevation myocardial infarction protocol. Circ Cardiovasc Qual Outcomes. 2009;2:508–13.
138. Pitta SR, Myers LA, Bjerke CM, et al. Using prehospital electrocardiograms to improve door-to-balloon time for transferred patients with ST-elevation myocardial infarction: a case of extreme performance. Circ Cardiovasc Qual Outcomes. 2010;3:93–7.
139. Daudelin DH, Sayah AJ, Kwong M, et al. Improving use of prehospital 12-lead ECG for early identification and treatment of acute coronary syndrome and ST-elevation myocardial infarction. Circ Cardiovasc Qual Outcomes. 2010;3:316–23.
140. Curtis JP, Herrin J, Bratzler DW, et al. Trends in race-based differences in door-to-balloon times. Arch Intern Med. 2010;170:992–3.
141. Krumholz HM, Herrin J, Miller LE, et al. Improvements in door-to-balloon time in the United States, 2005 to 2010. Circulation. 2011;124:1038–45.
142. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet. 2002;360:825–9.
143. Castaigne AD, Hervé C, Duval-Moulin AM, et al. Prehospital use of APSAC: results of a placebo-controlled study. Am J Cardiol. 1989;64:30A--33A; discussion 41A--42A.
144. Danchin N, Blanchard D, Steg PG, et al. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: results from the French Nationwide USIC 2000 Registry. Circulation. 2004;110:1909–15.

145. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med. 1993;329:383–9.
146. Roth A, Barbash GI, Hod H, et al. Should thrombolytic therapy be administered in the mobile intensive care unit in patients with evolving myocardial infarction? A pilot study. J Am Coll Cardiol. 1990;15:932–6.
147. Schofer J, Büttner J, Geng G, et al. Prehospital thrombolysis in acute myocardial infarction. Am J Cardiol. 1990;66:1429–33.
148. Björklund E, Stenestrand U, Lindbäck J, et al. Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. Eur Heart J. 2006;27:1146–52.
149. Morrow DA, Antman EM, Sayah A, et al. Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction: results of The Early Retavase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 trial. J Am Coll Cardiol. 2002;40:71–7.
150. Pedley DK, Bissett K, Connolly EM, et al. Prospective observational cohort study of time saved by prehospital thrombolysis for ST elevation myocardial infarction delivered by paramedics. BMJ. 2003;327:22–6.
151. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy: the Myocardial Infarction Triage and Intervention Trial. JAMA. 1993;270:1211–6.
152. Welsh RC, Travers A, Senaratne M, et al. Feasibility and applicability of paramedic-based prehospital fibrinolysis in a large North American center. Am Heart J. 2006;152:1007–14.
153. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region Early Anistreplase Trial. BMJ. 1992;305:548–53.
154. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. JAMA. 2000;283:2686–92.
155. Westerhout CM, Bonnefoy E, Welsh RC, et al. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. Am Heart J. 2011;161:283–90.
156. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S768–86. Errata in: Circulation. 2011;124:e403 and Circulation. 2011;123:e237.
157. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.
158. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549–56. Erratum in: N Engl J Med. 2002;346:1756.
159. Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest: a policy statement from the American Heart Association. Circulation. 2010;121:709–29. Erratum in: Circulation. 2010;122:e439.
160. Bendz B, Eritsland J, Nakstad AR, et al. Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. Resuscitation. 2004;63:49–53.
161. Borger van der Burg AE, Bax JJ, Boersma E, et al. Impact of percutaneous coronary intervention or coronary artery bypass grafting on outcome after nonfatal cardiac arrest outside the hospital. Am J Cardiol. 2003;91:785–9.
162. Bulut S, Aengevaeren WR, Luijten HJ, et al. Successful out-of-hospital cardiopulmonary resuscitation: what is the optimal in-hospital treatment strategy? Resuscitation. 2000;47:155–61.
163. Garot P, Lefevre T, Eltchaninoff H, et al. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. Circulation. 2007;115:1354–62.
164. Gorjup V, Radsel P, Kocjancic ST, et al. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. Resuscitation. 2007;72:379–85.
165. Hosmane VR, Mustafa NG, Reddy VK, et al. Survival and neurologic recovery in patients with ST-segment elevation myocardial infarction resuscitated from cardiac arrest. J Am Coll Cardiol. 2009;53:409–15.
166. Kahn JK, Glazier S, Swor R, et al. Primary coronary angioplasty for acute myocardial infarction complicated by out-of-hospital cardiac arrest. Am J Cardiol. 1995;75:1069–70.
167. Keelan PC, Bunch TJ, White RD, et al. Early direct coronary angioplasty in survivors of out-of-hospital cardiac arrest. Am J Cardiol. 2003;91:1461–3, A6.
168. Kern KB, Rahman O. Emergent percutaneous coronary intervention for resuscitated victims of out-of-hospital cardiac arrest. Catheter Cardiovasc Interv. 2010;75:616–24.
169. Marcusohn E, Markusohn E, Roguin A, et al. Primary percutaneous coronary intervention after out-of-hospital cardiac arrest: patients and outcomes. Isr Med Assoc J. 2007;9:257–9.
170. Pleskot M, Babu A, Hazukova R, et al. Out-of-hospital cardiac arrests in patients with acute ST elevation myocardial infarctions in the East Bohemian region over the period 2002–2004. Cardiology. 2008;109:41–51.
171. Quintero-Moran B, Moreno R, Villarreal S, et al. Percutaneous coronary intervention for cardiac arrest secondary to ST-elevation acute myocardial infarction: influence of immediate paramedical/medical assistance on clinical outcome. J Invasive Cardiol. 2006;18:269–72.
172. Richling N, Herkner H, Holzer M, et al. Thrombolytic therapy vs primary percutaneous intervention after ventricular fibrillation cardiac arrest due to acute ST-segment elevation myocardial infarction and its effect on outcome. Am J Emerg Med. 2007;25:545–50.
173. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997;336:1629–33.
174. Werling M, Thorén A-B, Axelsson C, et al. Treatment and outcome in post-resuscitation care after out-of-hospital cardiac arrest when a modern therapeutic approach was introduced. Resuscitation. 2007;73:40–5.
175. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010;121:e46–215. Errata in: Circulation. 2011;124:e425 and Circulation. 2010;121:e260.
176. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31. Erratum in: JAMA. 2008;300:1763.
177. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. 2004;44:1268–75.
178. Valenzuela TD, Roe DJ, Cretin S, et al. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation. 1997;96:3308–13.
179. Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "chain of survival" concept: a statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. Circulation. 1991;83:1832–47.
180. Larsen MP, Eisenberg MS, Cummins RO, et al. Predicting survival from out-of-hospital cardiac arrest: a graphic model. Ann Emerg Med. 1993;22:1652–8.
181. Weisfeldt ML, Sitlani CM, Ornato JP, et al. Survival after application of automatic external defibrillators before arrival of the emergency medical system: evaluation in the Resuscitation Outcomes Consortium population of 21 million. J Am Coll Cardiol. 2010;55:1713–20.
182. White RD, Hankins DG, Bugliosi TF. Seven years' experience with early defibrillation by police and paramedics in an emergency medical services system. Resuscitation. 1998;39:145–51.
183. Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. N Engl J Med. 2004;351:637–46.
184. Mosesso VN Jr, Newman MM, Ornato JP, et al. Law Enforcement Agency Defibrillation (LEA-D): proceedings of the National Center for Early Defibrillation Police AED Issues Forum. Prehosp Emerg Care. 2002;6:273–82.
185. Groh WJ, Lowe MR, Overgaard AD, et al. Attitudes of law enforcement officers regarding automated external defibrillators. Acad Emerg Med. 2002;9:751–3.
186. Koster RW. Automatic external defibrillator: key link in the chain of survival. J Cardiovasc Electrophysiol. 2002;13:S92–5.
187. Myerburg RJ, Fenster J, Velez M, et al. Impact of community-wide police car deployment of automated external defibrillators on survival from out-of-hospital cardiac arrest. Circulation. 2002;106:1058–64.
188. Ornato JP, McBurnie MA, Nichol G, et al. The Public Access Defibrillation (PAD) trial: study design and rationale. Resuscitation. 2003;56:135–47.

189. Caffrey SL, Willoughby PJ, Pepe PE, et al. Public use of automated external defibrillators. N Engl J Med. 2002;347:1242–7.
190. Donaldson E, Pearn J. First aid in the air. Aust N Z J Surg. 1996;66:431–4.
191. Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. N Engl J Med. 2000;343:1210–6.
192. Valenzuela TD, Roe DJ, Nichol G, et al. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med. 2000;343:1206–9.
193. Karch SB, Graff J, Young S, et al. Response times and outcomes for cardiac arrests in Las Vegas casinos. Am J Emerg Med. 1998;16:249–53.
194. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. Resuscitation. 2007;75:252–9.
195. Castrejón S, Cortés M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. Rev Esp Cardiol. 2009; 62:733–41.
196. Ornato JP, Peberdy MA, Tadler SC, et al. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the second national registry of myocardial infarction in the US. Resuscitation. 2001;48:117–23.
197. Lettieri C, Savonitto S, De Servi S, et al. Emergency percutaneous coronary intervention in patients with ST-elevation myocardial infarction complicated by out-of-hospital cardiac arrest: early and medium-term outcome. Am Heart J. 2009;157:569–75.e1.
198. Reynolds JC, Callaway CW, El Khoudary SR, et al. Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted analysis. J Intensive Care Med. 2009;24:179–86.
199. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med. 1984;310:1137–40.
200. Bangalore S, Hochman JS. A routine invasive strategy for out-of-hospital cardiac arrest survivors: are we there yet? Circ Cardiovasc Interv. 2010;3:197–9.
201. Field JM, Hazinski MF, Sayre MR, et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122: S640–56.
202. Nolan JP, Soar J. Post resuscitation care: time for a care bundle? Resuscitation. 2008;76:161–2.
203. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73:29–39.
204. McMullan PW Jr, White CJ. Doing what's right for the resuscitated. Catheter Cardiovasc Interv. 2010;76:161–3.
205. Holmes DR, Selzer F, Johnston JM, et al. Modeling and risk prediction in the current era of interventional cardiology: a report from the National Heart, Lung, and Blood Institute Dynamic Registry. Circulation. 2003;107:1871–6.
206. Matheny ME, Ohno-Machado L, Resnic FS. Discrimination and calibration of mortality risk prediction models in interventional cardiology. J Biomed Inform. 2005;38:367–75.
207. Resnic FS, Normand S-LT, Piemonte TC, et al. Improvement in mortality risk prediction after percutaneous coronary intervention through the addition of a "compassionate use" variable to the National Cardiovascular Data Registry CathPCI Dataset: a study from the Massachusetts Angioplasty Registry. J Am Coll Cardiol. 2011;57:904–11.
208. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med. 1999;341:1413–9.
209. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med. 1997;336:1621–8. Erratum in: N Engl J Med. 1997;337:287.
210. Grzybowski M, Clements EA, Parsons L, et al. Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: a propensity analysis. JAMA. 2003;290:1891–8.
211. Zahn R, Schuster S, Schiele R, et al; Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. Comparison of primary angioplasty with conservative therapy in patients with acute myocardial infarction and contraindications for thrombolytic therapy. Catheter Cardiovasc Interv. 1999;46:127–33.
212. Hochman JS, Sleeper LA, Webb JG, et al; for the SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med. 1999;341:625–34.
213. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med. 2006;355:2395–407.
214. Thune JJ, Hoefsten DE, Lindholm MG, et al. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. Circulation. 2005;112:2017–21.
215. Wu AH, Parsons L, Every NR, et al. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol. 2002;40:1389–94.
216. Hannan EL, Samadashvili Z, Walford G, et al. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. JACC Cardiovasc Interv. 2010;3:22–31.
217. Toma M, Buller CE, Westerhout CM, et al. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. Eur Heart J. 2010;31:1701–7.
218. Vlaar PJ, Mahmoud KD, Holmes DR Jr, et al. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. J Am Coll Cardiol. 2011;58:692–703.
219. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:e574–e651.
220. Niccoli G, Burzotta F, Galiuto L, et al. Myocardial no-reflow in humans. J Am Coll Cardiol. 2009;54:281–92.
221. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet. 2008;371:1915–20.
222. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med. 2008;358: 557–67.
223. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA. 2012;307:1817–26.
224. Kornowski R, Mehran R, Dangas G, et al. Prognostic impact of staged versus "one-time" multivessel percutaneous intervention in acute myocardial infarction: analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol. 2011;58:704–11.
225. Qarawani D, Nahir M, Abboud M, et al. Culprit only versus complete coronary revascularization during primary PCI. Int J Cardiol. 2008;123:288–92.
226. Khattab AA, Abdel-Wahab M, Röther C, et al. Multi-vessel stenting during primary percutaneous coronary intervention for acute myocardial infarction: a single-center experience. Clin Res Cardiol. 2008;97:32–8.
227. Varani E, Balducelli M, Aquilina M, et al. Single or multivessel percutaneous coronary intervention in ST-elevation myocardial infarction patients. Catheter Cardiovasc Interv. 2008;72:927–33.
228. Navarese EP, De Servi S, Buffon A, et al. Clinical impact of simultaneous complete revascularization vs. culprit only primary angioplasty in patients with ST-elevation myocardial infarction and multivessel disease: a meta-analysis. J Thromb Thrombolysis. 2011;31:217–25.
229. Bangalore S, Kumar S, Poddar KL, et al. Meta-analysis of multivessel coronary artery revascularization versus culprit-only revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease. Am J Cardiol. 2011;107:1300–10.
230. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med. 2000;343:915–22.
231. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. Circulation. 1985;71:699–708.

232. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA. 2007;297:1985–91.
233. Madsen JK, Grande P, Saunamäki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI): DANish trial in Acute Myocardial Infarction. Circulation. 1997;96:748–55.
234. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. Eur Heart J. 2008;29: 2989–3001.
235. Sardella G, Mancone M, Bucciarelli-Ducci C, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention) prospective, randomized trial. J Am Coll Cardiol. 2009;53:309–15.
236. Ali A, Cox D, Dib N, et al. Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. J Am Coll Cardiol. 2006;48:244–52.
237. Migliorini A, Stabile A, Rodriguez AE, et al. Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction: the JET-STENT trial. J Am Coll Cardiol. 2010;56:1298–306.
238. Nordmann AJ, Hengstler P, Harr T, et al. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. Am J Med. 2004;116:253–62.
239. Zhu MM, Feit A, Chadow H, et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. Am J Cardiol. 2001;88:297–301.
240. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation. 2006;113:2803–9.
241. Kałuza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol. 2000;35:1288–94.
242. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation. 2007;115:813–8.
243. Park D-W, Park S-W, Park K-H, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol. 2006;98:352–6.
244. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation. 2004;109:1930–2.
245. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006;48:2584–91.
246. Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. Catheter Cardiovasc Interv. 2005;65:516–9.
247. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. Eur Heart J. 2007;28:2706–13.
248. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;358:2218–30.
249. Räber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. Circulation. 2011;123:2819–28.
250. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012;379:1393–402.
251. Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. Eur Heart J. 2009;30:900–7.
252. Barnathan ES, Schwartz JS, Taylor L, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation. 1987;76:125–34.
253. Mehta SR, Bassand J-P, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363:930–42. Erratum in: N Engl J Med. 2010;363:1585.
254. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86. Erratum in: BMJ. 2002;324:141.
255. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084–9.
256. Deleted in press.
257. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124: 2458–73.
258. Patti G, Bárczi G, Orlic D, et al. Outcome comparison of 600- and 300-mg loading doses of clopidogrel in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results from the ARMYDA-6 MI (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Myocardial Infarction) randomized study. J Am Coll Cardiol. 2011;58:1592–9.
259. Mehta SR, Tanguay J-F, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet. 2010;376:1233–43.
260. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357:2001–15.
261. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010;122:2131–41.
262. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009;373:723–31.
263. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol. 2005; 95:1218–22.
264. Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med. 2009;150:379–86.
265. Brener SJ, Barr LA, Burchenal JE, et al; for the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation. 1998;98:734–41.
266. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002;346:957–66.
267. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344:1895–903.
268. ten Berg JM, van 't Hof AWJ, Dill T, et al. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. J Am Coll Cardiol. 2010;55:2446–55.
269. Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. JAMA. 2008;299:1788–99.
270. Akerblom A, James SK, Koutouzis M, et al. Eptifibatide is noninferior to abciximab in primary percutaneous coronary intervention: results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). J Am Coll Cardiol. 2010;56:470–5.

271. Ellis SG, Tendera M, de Belder MA, et al. 1-Year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. JACC Cardiovasc Interv. 2009;2:909–16.
272. Montalescot G, Borentain M, Payot L, et al. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. JAMA. 2004;292:362–6.
273. Maioli M, Bellandi F, Leoncini M, et al. Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAx-AMI Trial). J Am Coll Cardiol. 2007;49:1517–24.
274. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet. 2006;367:579–88. Erratum in: Lancet. 2006;367:1656.
275. Van't Hof AWJ, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet. 2008;372:537–46.
276. El Khoury C, Dubien P-Y, Mercier C, et al. Prehospital high-dose tirofiban in patients undergoing primary percutaneous intervention: the AGIR-2 study. Arch Cardiovasc Dis. 2010;103:285–92.
277. De Luca G, Bellandi F, Huber K, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. J Thromb Haemost. 2011;9:2361–70.
278. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. Circulation. 2009;119:1933–40.
279. Bellandi F, Maioli M, Gallopin M, et al. Increase of myocardial salvage and left ventricular function recovery with intracoronary abciximab downstream of the coronary occlusion in patients with acute myocardial infarction treated with primary coronary intervention. Catheter Cardiovasc Interv. 2004;62:186–92.
280. Romagnoli E, Burzotta F, Trani C, et al. Angiographic evaluation of the effect of intracoronary abciximab administration in patients undergoing urgent PCI. Int J Cardiol. 2005;105:250–5.
281. Iversen A, Galatius S, Jensen JS. The optimal route of administration of the glycoprotein IIb/IIIa receptor antagonist abciximab during percutaneous coronary intervention: intravenous versus intracoronary. Curr Cardiol Rev. 2008;4:293–9.
282. Kakkar AK, Moustapha A, Hanley HG, et al. Comparison of intracoronary vs. intravenous administration of abciximab in coronary stenting. Catheter Cardiovasc Interv. 2004;61:31–4.
283. Wöhrle J, Grebe OC, Nusser T, et al. Reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. Circulation. 2003;107:1840–3.
284. Bertrand OF, Rodés-Cabau J, Larose E, et al. Intracoronary compared to intravenous abciximab and high-dose bolus compared to standard dose in patients with ST-segment elevation myocardial infarction undergoing transradial primary percutaneous coronary intervention: a two-by-two factorial placebo-controlled randomized study. Am J Cardiol. 2010;105:1520–7.
285. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–62.
286. Collet J-P, Hulot J-S, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009;373:309–17.
287. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009;30:916–22.
288. Giusti B, Gori AM, Marcucci R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol. 2009;103:806–11.
289. Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation. 2010;122:537–57.
290. Paré G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med. 2010;363:1704–14.
291. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363:1909–17.
292. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet. 2009;374:989–97.
293. AstraZeneca. Brilinta REMS Document. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM264004.pdf. Accessed July 26, 2012.
294. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
295. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2011;124:544–54.
296. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360:2066–78.
297. Diener H-C, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:331–7.
298. Sacco RL, Diener H-C, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359:1238–51.
299. James SK, Storey RF, Khurmi NS, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. Circulation. 2012;125:2914–21.
300. Verheugt FWA. Beware of novel antiplatelet therapy in acute coronary syndrome patients with previous stroke. Circulation. 2012;125:2821–3.
301. Shimada YJ, Nakra NC, Fox JT, et al. Meta-analysis of prospective randomized controlled trials comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol. 2012;109:624–8.
302. Gu YL, Kampinga MA, Wieringa WG, et al. Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction (CICERO) trial. Circulation. 2010;122:2709–17.
303. Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. Lancet. 2012;379:923–31.
304. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA. 2006;295:1519–30.
305. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet. 2011;378:693–703.
306. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet. 1988;1:545–9.
307. EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. Lancet. 1993;342:767–72.
308. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet. 1988;2:349–60.
309. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. Lancet. 1993;342:759–66.
310. Rossi P, Bolognese L. Comparison of intravenous urokinase plus heparin versus heparin alone in acute myocardial infarction: Urochinasi per via Sistemica nell'Infarto Miocardico (USIM) Collaborative Group. Am J Cardiol. 1991;68:585–92.

311. The I.S.A.M. Study Group. A prospective trial of Intravenous Streptokinase in Acute Myocardial infarction (I.S.A.M.): mortality, morbidity, and infarct size at 21 days. N Engl J Med. 1986;314:1465–71.
312. The TIMI IIIA Investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest: results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. Circulation. 1993;87:38–52.
313. Barrabés JA, Figueras J, Moure C, et al. Prognostic value of lead aVR in patients with a first non-ST-segment elevation acute myocardial infarction. Circulation. 2003;108:814–9.
314. Bode C, Smalling RW, Berg G, et al; RAPID II Investigators. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. Circulation. 1996;94:891–8.
315. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet. 1992;339:753–70.
316. Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. JAMA. 2001;286:442–9.
317. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med. 1997;337:1118–23.
318. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673–82.
319. Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet. 1999;354:716–22.
320. Wilcox RG, von der Lippe G, Olsson CG, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet. 1988;2:525–30.
321. Bonnefoy E, Godon P, Kirkorian G, et al. Significance of serum troponin I elevation in patients with acute aortic dissection of the ascending aorta. Acta Cardiol. 2005;60:165–70.
322. Langer A, Goodman SG, Topol EJ, et al; LATE Study Investigators. Late assessment of thrombolytic efficacy (LATE) study: prognosis in patients with non-Q wave myocardial infarction. J Am Coll Cardiol. 1996;27:1327–32.
323. Terkelsen CJ, Lassen JF, Nørgaard BL, et al. Are we underestimating the full potential of early thrombolytic treatment in patients with acute myocardial infarction? Heart. 2003;89:483–4.
324. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med. 1993;329:1615–22. Erratum in: N Engl J Med. 1994;330:516.
325. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction: current status and new horizons for pharmacological reperfusion, part 1. Circulation. 2001;103:2862–6.
326. Neuhaus KL, von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC patency study (TAPS). J Am Coll Cardiol. 1992;19:885–91.
327. Deleted in press.
328. Cannon CP, McCabe CH, Gibson CM, et al. TNK-tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 10A dose-ranging trial. Circulation. 1997;95:351–6.
329. Martin GV, Sheehan FH, Stadius M, et al. Intravenous streptokinase for acute myocardial infarction: effects on global and regional systolic function. Circulation. 1988;78:258–66.
330. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1607–21.
331. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352:1179–89.
332. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med. 2006;354:1477–88.
333. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet. 2001;358:605–13.
334. Ross AM, Molhoek P, Lundergan C, et al. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). Circulation. 2001;104:648–52.
335. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. Circulation. 2002;105:1642–9. Erratum in: Circulation. 2002;105:2799.
336. Eisenberg PR. Role of heparin in coronary thrombolysis. Chest. 1992;101:131S--9S.
337. de Bono DP, Simoons ML, Tijssen J, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. Br Heart J. 1992;67:122–8.
338. Thompson PL, Aylward PE, Federman J, et al; for the National Heart Foundation of Australia Coronary Thrombolysis Group. A randomized comparison of intravenous heparin with oral aspirin and dipyridamole 24 hours after recombinant tissue-type plasminogen activator for acute myocardial infarction. Circulation. 1991;83:1534–42.
339. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. Circulation. 1996;93:870–8.
340. Fox KAA, Antman EM, Montalescot G, et al. The impact of renal dysfunction on outcomes in the ExTRACT-TIMI 25 trial. J Am Coll Cardiol. 2007;49:2249–55.
341. Peters RJG, Joyner C, Bassand J-P, et al. The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. Eur Heart J. 2008;29:324–31.
342. White H. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet. 2001;358:1855–63.
343. Vogt A, von Essen R, Tebbe U, et al. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. J Am Coll Cardiol. 1993;21:1391–5.
344. Gibson CM, Murphy SA, Rizzo MJ, et al; Thrombolysis In Myocardial Infarction (TIMI) Study Group. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Circulation. 1999;99:1945–50.
345. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002;105:1909–13.
346. Sutton AGC, Campbell PG, Graham R, et al. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. J Am Coll Cardiol. 2004;44:287–96.
347. Sutton AG, Campbell PG, Price DJ, et al. Failure of thrombolysis by streptokinase: detection with a simple electrocardiographic method. Heart. 2000;84:149–56.
348. Fernandez AR, Sequeira RF, Chakko S, et al. ST segment tracking for rapid determination of patency of the infarct-related artery in acute myocardial infarction. J Am Coll Cardiol. 1995;26:675–83.
349. de Lemos JA, Antman EM, Giugliano RP, et al; Thrombolysis in Myocardial Infarction (TIMI) 14 Investigators. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Am J Cardiol. 2000;85:299–304.
350. Zeymer U, Schröder R, Tebbe U, et al. Non-invasive detection of early infarct vessel patency by resolution of ST-segment elevation in patients with thrombolysis for acute myocardial infarction: results of the angiographic substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 trial. Eur Heart J. 2001;22:769–75.
351. Cooper HA, de Lemos JA, Morrow DA, et al. Minimal ST-segment deviation: a simple, noninvasive method for identifying patients with a patent infarction-related artery after fibrinolytic administration. Am Heart J. 2002;144:790–5.

352. Purcell IF, Newall N, Farrer M. Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. Heart. 1997;78:465–71.
353. Schröder R, Wegscheider K, Schröder K, et al. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens: a substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol. 1995;26:1657–64.
354. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. JAMA. 2001;285:190–2.
355. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med. 2005;353:2758–68.
356. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. J Am Coll Cardiol. 2007;49:422–30.
357. Collet J-P, Montalescot G, Le May M, et al. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. J Am Coll Cardiol. 2006;48:1326–35.
358. Bøhmer E, Hoffmann P, Abdelnoor M, et al. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J Am Coll Cardiol. 2010;55:102–10.
359. Borgia F, Goodman SG, Halvorsen S, et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J. 2010;31:2156–69.
360. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360:2705–18.
361. Di Mario C, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. Lancet. 2008;371:559–68.
362. Fernandez-Avilés F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet. 2004;364:1045–53.
363. White HD. Systems of care: need for hub-and-spoke systems for both primary and systematic percutaneous coronary intervention after fibrinolysis. Circulation. 2008;118:219–22.
364. Appleton DL, Abbate A, Biondi-Zoccai GGL. Late percutaneous coronary intervention for the totally occluded infarct-related artery: a meta-analysis of the effects on cardiac function and remodeling. Catheter Cardiovasc Interv. 2008;71:772–81.
365. Danchin N, Coste P, Ferrières J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the French registry on Acute ST-elevation Myocardial Infarction (FAST-MI). Circulation. 2008;118:268–76.
366. Gibson CM, Karha J, Murphy SA, et al. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis In Myocardial Infarction trials. J Am Coll Cardiol. 2003;42:7–16.
367. Stenestrand U, Wallentin L. Early revascularisation and 1-year survival in 14-day survivors of acute myocardial infarction: a prospective cohort study. Lancet. 2002;359:1805–11.
368. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J. 2006;27:1530–8.
369. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol. 2005;46:417–24.
370. Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol. 2003;42:634–41.
370a. Granger CB. Who should have a routine early invasive approach after fibrinolytic therapy? Eur Heart J. 2011;32:1961-3.
371. Thiele H, Engelmann L, Elsner K, et al. Comparison of pre-hospital combination-fibrinolysis plus conventional care with pre-hospital combination-fibrinolysis plus facilitated percutaneous coronary intervention in acute myocardial infarction. Eur Heart J. 2005;26:1956–63.
372. Steg PG, Kerner A, Van de Werf F, et al. Impact of in-hospital revascularization on survival in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. Circulation. 2008;118:1163–71.
373. Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004;109:494–9.
374. D'Souza SP, Mamas MA, Fraser DG, et al. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. Eur Heart J. 2011;32:972–82.
375. Gupta M, Chang W-C, Van de Werf F, et al. International differences in in-hospital revascularization and outcomes following acute myocardial infarction: a multilevel analysis of patients in ASSENT-2. Eur Heart J. 2003;24:1640–50.
376. Ioannidis JPA, Katritsis DG. Percutaneous coronary intervention for late reperfusion after myocardial infarction in stable patients. Am Heart J. 2007;154:1065–71.
377. Steg PG, Thuaire C, Himbert D, et al. DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction. Eur Heart J. 2004;25:2187–94.
378. Wilson SH, Bell MR, Rihal CS, et al. Infarct artery reocclusion after primary angioplasty, stent placement, and thrombolytic therapy for acute myocardial infarction. Am Heart J. 2001;141:704–10.
379. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295:2511–5.
380. Hochman JS, Reynolds HR, Dzavík V, et al. Long-term effects of percutaneous coronary intervention of the totally occluded infarct-related artery in the subacute phase after myocardial infarction. Circulation. 2011;124:2320–8.
381. Jaski BE, Cohen JD, Trausch J, et al. Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: comparison of single-vessel versus multivessel coronary artery disease. Am Heart J. 1992;124:1427–33.
382. Muller DW, Topol EJ, Ellis SG, et al; Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. Multivessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Am Heart J. 1991;121:1042–9.
383. Corpus RA, House JA, Marso SP, et al. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. Am Heart J. 2004;148:493–500.
384. Rigattieri S, Biondi-Zoccai G, Silvestri P, et al. Management of multivessel coronary disease after ST elevation myocardial infarction treated by primary angioplasty. J Interv Cardiol. 2008;21:1–7.
385. Ntalianis A, Sels J-W, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv. 2010;3:1274–81.
386. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial. J Am Coll Cardiol. 1998;32:2003–10.
387. Ohman EM, Kleiman NS, Gacioch G, et al; IMPACT-AMI Investigators. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction: results of a randomized, placebo-controlled, dose-ranging trial. Circulation. 1997;95:846–54.
388. Deleted in press.
389. Ronner E, van Domburg RT, van den Brand MJBM, et al. Platelet GP IIb/IIIa receptor blockers for failed thrombolysis in acute myocardial infarction, alone or as adjunct to other rescue therapies: single centre retrospective analysis of 548 consecutive patients with acute myocardial infarction. Eur Heart J. 2002;23:1529–37.

390. Gibson CM, Murphy SA, Montalescot G, et al. Percutaneous coronary intervention in patients receiving enoxaparin or unfractionated heparin after fibrinolytic therapy for ST-segment elevation myocardial infarction in the ExTRACT-TIMI 25 trial. J Am Coll Cardiol. 2007;49:2238–46.
391. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. Circulation. 1995;91:2325–34.
392. Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction: etiologies, management and outcome: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000;36:1063–70.
393. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e652–735.
394. Dalrymple-Hay MJ, Langley SM, Sami SA, et al. Should coronary artery bypass grafting be performed at the same time as repair of a post-infarct ventricular septal defect? Eur J Cardiothorac Surg. 1998;13:286–92.
395. Menon V, Webb JG, Hillis LD, et al. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? J Am Coll Cardiol. 2000;36:1110–6.
396. Slater J, Brown RJ, Antonelli TA, et al. Cardiogenic shock due to cardiac free-wall rupture or tamponade after acute myocardial infarction: a report from the SHOCK Trial Registry: Should we emergently revascularize occluded coronaries for cardiogenic shock? J Am Coll Cardiol. 2000;36:1117–22.
397. Tavakoli R, Weber A, Vogt P, et al. Surgical management of acute mitral valve regurgitation due to post-infarction papillary muscle rupture. J Heart Valve Dis. 2002;11:20–5
398. Thompson CR, Buller CE, Sleeper LA, et al. Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry: SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? J Am Coll Cardiol. 2000;36:1104–9.
399. Jacob M, Smedira N, Blackstone E, et al. Effect of timing of chronic preoperative aspirin discontinuation on morbidity and mortality in coronary artery bypass surgery. Circulation. 2011;123:577–83.
400. Kim JH-J, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. Am Heart J. 2008;156:886–92.
401. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011;57:672–84.
402. Nijjer SS, Watson G, Athanasiou T, et al. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. Eur Heart J. 2011;32:2970–88.
403. Barker CM, Anderson HV. Acute coronary syndromes: don't bypass the clopidogrel. J Am Coll Cardiol. 2009;53:1973–4.
404. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol. 2009;53:1965–72.
405. Bizzarri F, Scolletta S, Tucci E, et al. Perioperative use of tirofiban hydrochloride (Aggrastat) does not increase surgical bleeding after emergency or urgent coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2001;122:1181–5.
406. Dyke CM, Bhatia D, Lorenz TJ, et al. Immediate coronary artery bypass surgery after platelet inhibition with eptifibatide: results from PURSUIT. Ann Thorac Surg. 2000;70:866–71; discussion 871–2.
407. Shim JK, Choi YS, Oh YJ, et al. Effects of preoperative aspirin and clopidogrel therapy on perioperative blood loss and blood transfusion requirements in patients undergoing off-pump coronary artery bypass graft surgery. J Thorac Cardiovasc Surg. 2007;134:59–64.
408. Woo YJ, Grand T, Valettas N. Off-pump coronary artery bypass grafting attenuates postoperative bleeding associated with preoperative clopidogrel administration. Heart Surg Forum. 2003;6:282–5.
409. Maltais S, Perrault LP, Do Q-B. Effect of clopidogrel on bleeding and transfusions after off-pump coronary artery bypass graft surgery: impact of discontinuation prior to surgery. Eur J Cardiothorac Surg. 2008;34:127–31.
410. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502. Errata in: N Engl J Med. 2001;345:1716 and N Engl J Med. 2001;345:1506.
411. Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol. 2002;40:231–7.
412. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. Crit Care Med. 2001;29:2271–5.
413. Firanescu CE, Martens EJ, Schönberger JPAM, et al. Postoperative blood loss in patients undergoing coronary artery bypass surgery after preoperative treatment with clopidogrel: a prospective randomised controlled study. Eur J Cardiothorac Surg. 2009;36:856–62.
414. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1622–32.
415. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) II-B Study. Circulation. 1991;83:422–37.
416. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. Lancet. 1986;2:57–66.
417. A randomized trial of propranolol in patients with acute myocardial infarction, I: mortality results. JAMA. 1982;247:1707–14.
418. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730–7.
419. Deleted in press.
420. Pfeffer MA, Braunwald E, Moyé LA, et al; the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med. 1992;327:669–77.
421. Ball SG, Hall AS, Murray GD. ACE inhibition, atherosclerosis and myocardial infarction: the AIRE Study in practice: Acute Infarction Ramipril Efficacy Study. Eur Heart J. 1994;15 Suppl B:20–5; discussion 26–30.
422. Køber L, Torp-Pedersen C, Carlsen JE, et al; Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 1995;333:1670–6.
423. Pfeffer MA, Greaves SC, Arnold JM, et al. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction: the healing and early afterload reducing therapy trial. Circulation. 1997;95:2643–51.
424. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893–906. Erratum in: N Engl J Med. 2004;350:203.
425. Maggioni AP, Fabbri G. VALIANT (VALsartan In Acute myocardial iNfarcTion) trial. Expert Opin Pharmacother. 2005;6:507–12.
426. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–21. Erratum in: N Engl J Med. 2003;348:2271.
427. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. Circulation. 1998;97:2202–12.
428. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343:1115–22.
429. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995;345:669–85.
430. Cleland JG, Erhardt L, Murray G, et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE Study Investigators. Eur Heart J. 1997;18:41–51.

431. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial: Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002;360:752–60.
432. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004; 351:2058–68.
433. Adamopoulos C, Ahmed A, Fay R, et al. Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHESUS trial. Eur J Heart Fail. 2009;11:1099–105.
434. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48:438–45.
435. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
436. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–504. Erratum in: N Engl J Med. 2006;354:778.
437. Sacks FM, Pfeffer MA, Moye LA, et al; Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996;335:1001–9.
438. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
439. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307–16.
440. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285:1711–8.
441. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm. Accessed May 18, 2012.
442. Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol. 2008;52:914–20.
443. Lee KH, Jeong MH, Kim HM, et al. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. J Am Coll Cardiol. 2011;58:1664–71.
444. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA expert consensus document: use of sildenafil (Viagra) in patients with cardiovascular disease. Circulation. 1999;99:168–77. Erratum in: J Am Coll Cardiol. 1999;34:1850.
445. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. BMJ. 1989;299: 1187–92.
446. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995; 92:1326–31.
447. McNulty PH, King N, Scott S, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. Am J Physiol Heart Circ Physiol. 2005;288:H1057–62.
448. Gibson CM, Pride YB, Aylward PE, et al. Association of non-steroidal anti-inflammatory drugs with outcomes in patients with ST-segment elevation myocardial infarction treated with fibrinolytic therapy: an ExTRACT-TIMI 25 analysis. J Thromb Thrombolysis. 2009;27:11–7.
449. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation. 2006;113:2906–13.
450. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ. 2006;332:1302–8.
451. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006;296:1633–44.
452. Babaev A, Frederick PD, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA. 2005;294:448–54.
453. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000;102:2031–7.
454. French JK, Feldman HA, Assmann SF, et al. Influence of thrombolytic therapy, with or without intra-aortic balloon counterpulsation, on 12-month survival in the SHOCK trial. Am Heart J. 2003;146:804–10.
455. Barron HV, Every NR, Parsons LS, et al. The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: data from the National Registry of Myocardial Infarction 2. Am Heart J. 2001;141:933–9.
456. Chen EW, Canto JG, Parsons LS, et al. Relation between hospital intra-aortic balloon counterpulsation volume and mortality in acute myocardial infarction complicated by cardiogenic shock. Circulation. 2003;108:951–7.
457. Sanborn TA, Sleeper LA, Bates ER, et al. Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000;36:1123–9.
458. Sjauw KD, Engström AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? Eur Heart J. 2009;30:459–68.
459. Ohman EM, Nanas J, Stomel RJ, et al. Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial. J Thromb Thrombolysis. 2005;19:33–9.
460. Dzavik V, Sleeper LA, Cocke TP, et al. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: a report from the SHOCK Trial Registry. Eur Heart J. 2003;24:828–37.
461. Dauerman HL, Goldberg RJ, Malinski M, et al. Outcomes and early revascularization for patients > or = 65 years of age with cardiogenic shock. Am J Cardiol. 2001;87:844–8.
462. Dauerman HL, Ryan TJ Jr, Piper WD, et al. Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter, decade-long experience. J Invasive Cardiol. 2003;15:380–4.
463. Kar B, Gregoric ID, Basra SS, et al. The percutaneous ventricular assist device in severe refractory cardiogenic shock. J Am Coll Cardiol. 2011;57:688–96.
464. Thiele H, Smalling RW, Schuler GC. Percutaneous left ventricular assist devices in acute myocardial infarction complicated by cardiogenic shock. Eur Heart J. 2007;28:2057–63.
465. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89.
466. Robalino BD, Whitlow PL, Underwood DA, et al. Electrocardiographic manifestations of right ventricular infarction. Am Heart J. 1989; 118:138–44.
467. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation. 2003;108:1146–62.
468. Kinch JW, Ryan TJ. Right ventricular infarction. N Engl J Med. 1994;330:1211–7.
469. Wellens HJ. The value of the right precordial leads of the electrocardiogram. N Engl J Med. 1999;340:381–3.
470. Tanimoto T, Imanishi T, Kitabata H, et al. Prevalence and clinical significance of papillary muscle infarction detected by late gadolinium-enhanced magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. Circulation. 2010;122:2281–7.

471. Yosefy C, Beeri R, Guerrero JL, et al. Mitral regurgitation after anteroapical myocardial infarction: new mechanistic insights. Circulation. 2011;123:1529–36.
472. Tepe NA, Edmunds LH Jr. Operation for acute postinfarction mitral insufficiency and cardiogenic shock. J Thorac Cardiovasc Surg. 1985;89:525–30.
473. Chen Q, Darlymple-Hay MJ, Alexiou C, et al. Mitral valve surgery for acute papillary muscle rupture following myocardial infarction. J Heart Valve Dis. 2002;11:27–31.
474. Kishon Y, Oh JK, Schaff HV, et al. Mitral valve operation in postinfarction rupture of a papillary muscle: immediate results and long-term follow-up of 22 patients. Mayo Clin Proc. 1992;67:1023–30.
475. Fasol R, Lakew F, Wetter S. Mitral repair in patients with a ruptured papillary muscle. Am Heart J. 2000;139:549–54.
476. Nishimura RA, Gersh BJ, Schaff HV. The case for an aggressive surgical approach to papillary muscle rupture following myocardial infarction: "from paradise lost to paradise regained." Heart. 2000;83:611–3.
477. Crenshaw BS, Granger CB, Birnbaum Y, et al; GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) Trial Investigators. Risk factors, angiographic patterns, and outcomes in patients with ventricular septal defect complicating acute myocardial infarction. Circulation. 2000;101:27–32.
478. Prêtre R, Ye Q, Grünenfelder J, et al. Operative results of "repair" of ventricular septal rupture after acute myocardial infraction. Am J Cardiol. 1999;84:785–8.
479. Lemery R, Smith HC, Giuliani ER, et al. Prognosis in rupture of the ventricular septum after acute myocardial infarction and role of early surgical intervention. Am J Cardiol. 1992;70:147–51.
480. Skillington PD, Davies RH, Luff AJ, et al. Surgical treatment for infarct-related ventricular septal defects: improved early results combined with analysis of late functional status. J Thorac Cardiovasc Surg. 1990;99:798–808.
481. Topaz O, Taylor AL. Interventricular septal rupture complicating acute myocardial infarction: from pathophysiologic features to the role of invasive and noninvasive diagnostic modalities in current management. Am J Med. 1992;93:683–8.
482. Westaby S, Parry A, Ormerod O, et al. Thrombolysis and postinfarction ventricular septal rupture. J Thorac Cardiovasc Surg. 1992;104:1506–9.
483. Muehrcke DD, Daggett WM Jr, Buckley MJ, et al. Postinfarct ventricular septal defect repair: effect of coronary artery bypass grafting. Ann Thorac Surg. 1992;54:876–82; discussion 882–883.
484. Birnbaum Y, Chamoun AJ, Anzuini A, et al. Ventricular free wall rupture following acute myocardial infarction. Coron Artery Dis. 2003;14:463–70.
485. Becker RC, Gore JM, Lambrew C, et al. A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction. J Am Coll Cardiol. 1996;27:1321–6.
486. Honan MB, Harrell FE Jr, Reimer KA, et al. Cardiac rupture, mortality and the timing of thrombolytic therapy: a meta-analysis. J Am Coll Cardiol. 1990;16:359–67.
487. McMullan MH, Maples MD, Kilgore TL Jr, et al. Surgical experience with left ventricular free wall rupture. Ann Thorac Surg. 2001;71:1894–8; discussion 1898–9.
488. Newby KH, Thompson T, Stebbins A, et al; the GUSTO Investigators. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: incidence and outcomes. Circulation. 1998;98:2567–73.
489. Mehta RH, Starr AZ, Lopes RD, et al. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. JAMA. 2009;301:1779–89.
490. 2010 Advanced Cardiac Life Support Guidelines. Available at: http://acls-algorithms.com/vfpulseless-vt. Accessed May 16, 2012.
491. Wever EF, Hauer RN, van Capelle FL, et al. Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. Circulation. 1995;91:2195–203.
492. Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). Am Heart J. 1994;127:1139–44.
493. Connolly SJ, Hallstrom AP, Cappato R, et al; for the AVID, CASH and CIDS studies: Antiarrhythmics vs Implantable Defibrillator study: Cardiac Arrest Study Hamburg: Canadian Implantable Defibrillator Study. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J. 2000;21:2071–8.
494. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576–83.
495. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101:1297–302.
496. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation. 2008;117:e350–408. Erratum in: Circulation. 2009;120:e34–5.
497. Lopes RD, Elliott LE, White HD, et al. Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial. Eur Heart J. 2009;30:2019–28.
498. Gao R, Zhang J, Cheng L, et al. A Phase II, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in patients with chronic heart failure. J Am Coll Cardiol. 2010;55:1907–14.
499. Califf RM, White HD, Van de Werf F, et al; GUSTO-I Investigators. One-year results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) trial. Circulation. 1996;94:1233–8.
500. Bloch Thomsen PE, Jons C, Raatikainen MJP, et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation. 2010;122:1258–64.
501. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology. Circulation. 2011;123:e269–367.
502. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369–429. Erratum in: Eur Heart J. 2011;32:1172.
503. Deleted in press.
504. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S729-67. Erratum in: Circulation. 2011;123:e236.
505. Hreybe H, Saba S. Location of acute myocardial infarction and associated arrhythmias and outcome. Clin Cardiol. 2009;32:274–7.
506. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005;149:1043–9.
507. Newby KH, Pisanó E, Krucoff MW, et al. Incidence and clinical relevance of the occurrence of bundle-branch block in patients treated with thrombolytic therapy. Circulation. 1996;94:2424–8.
508. Petrina M, Goodman SG, Eagle KA. The 12-lead electrocardiogram as a predictive tool of mortality after acute myocardial infarction: current status in an era of revascularization and reperfusion. Am Heart J. 2006;152:11–8.
509. Berman J, Haffajee CI, Alpert JS. Therapy of symptomatic pericarditis after myocardial infarction: retrospective and prospective studies of aspirin, indomethacin, prednisone, and spontaneous resolution. Am Heart J. 1981;101:750–3.
510. Bulkley BH, Roberts WC. Steroid therapy during acute myocardial infarction: a cause of delayed healing and of ventricular aneurysm. Am J Med. 1974;56:244–50.
511. Silverman HS, Pfeifer MP. Relation between use of anti-inflammatory agents and left ventricular free wall rupture during acute myocardial infarction. Am J Cardiol. 1987;59:363–4.
512. Imazio M, Negro A, Belli R, et al. Frequency and prognostic significance of pericarditis following acute myocardial infarction treated by primary percutaneous coronary intervention. Am J Cardiol. 2009;103:1525–9.

513. Orsinelli DA, Pearson AC. Usefulness of transesophageal echocardiography to screen for left atrial thrombus before elective cardioversion for atrial fibrillation. Am J Cardiol. 1993;72:1337–9.
514. Wall TC, Califf RM, Harrelson-Woodlief L, et al; the TAMI Study Group. Usefulness of a pericardial friction rub after thrombolytic therapy during acute myocardial infarction in predicting amount of myocardial damage. Am J Cardiol. 1990;66:1418–21.
515. Patel MR, Meine TJ, Lindblad L, et al. Cardiac tamponade in the fibrinolytic era: analysis of >100,000 patients with ST-segment elevation myocardial infarction. Am Heart J. 2006;151:316–22.
516. Hombach V, Grebe O, Merkle N, et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. Eur Heart J. 2005;26:549–57.
517. Gueret P, Khalife K, Jobic Y, et al. Echocardiographic assessment of the incidence of mechanical complications during the early phase of myocardial infarction in the reperfusion era: a French multicentre prospective registry. Arch Cardiovasc Dis. 2008;101:41–7.
518. López-Sendón J, Gurfinkel EP, Lopez de Sa E, et al. Factors related to heart rupture in acute coronary syndromes in the Global Registry of Acute Coronary Events. Eur Heart J. 2010;31:1449–56.
519. Figueras J, Juncal A, Carballo J, et al. Nature and progression of pericardial effusion in patients with a first myocardial infarction: relationship to age and free wall rupture. Am Heart J. 2002;144:251–8.
520. Figueras J, Barrabés JA, Serra V, et al. Hospital outcome of moderate to severe pericardial effusion complicating ST-elevation acute myocardial infarction. Circulation. 2010;122:1902–9.
521. Andreotti F, Testa L, Biondi-Zoccai GGL, et al. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J. 2006;27:519–26.
522. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e531S--e575S.
523. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e637S--68S. Erratum in: Chest. 2012;141:1129.
524. Lip GYH, Huber K, Andreotti F, et al. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary: a Consensus Document of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2010;31:1311–8.
525. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North-American perspective. Thromb Haemost. 2011;106:572–84.
526. Turpie AGG, Chin BSP, Lip GYH. Venous thromboembolism: pathophysiology, clinical features, and prevention. BMJ. 2002;325:887–90.
527. Ng TMH, Tsai F, Khatri N, et al. Venous thromboembolism in hospitalized patients with heart failure: incidence, prognosis, and prevention. Circ Heart Fail. 2010;3:165–73.
528. Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160:181–8.
529. Matsuo T, Tomaru T, Kario K, et al. Incidence of heparin-PF4 complex antibody formation and heparin-induced thrombocytopenia in acute coronary syndrome. Thromb Res. 2005;115:475–81.
530. Ohman EM, Granger CB, Rice L, et al. Identification, diagnosis and treatment of heparin-induced thrombocytopenia and thrombosis: a registry of prolonged heparin use and thrombocytopenia among hospitalized patients with and without cardiovascular disease: the Complication After Thrombocytopenia Caused by Heparin (CATCH) Registry Steering Committee. J Thromb Thrombolysis. 2005;19:11–9.
531. Crespo EM, Oliveira GBF, Honeycutt EF, et al. Evaluation and management of thrombocytopenia and suspected heparin-induced thrombocytopenia in hospitalized patients: the Complications After Thrombocytopenia Caused by Heparin (CATCH) Registry. Am Heart J. 2009;157:651–7.
532. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–9.
533. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet. 2009;374:1967–74.
534. Linkins L-A, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e495S--e530S.
535. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol. 2005;96:1200–6.
536. Spencer FA, Moscucci M, Granger CB, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation. 2007;116:2793–801.
537. Giugliano RP, Giraldez RR, Morrow DA, et al. Relations between bleeding and outcomes in patients with ST-elevation myocardial infarction in the ExTRACT-TIMI 25 trial. Eur Heart J. 2010;31:2103–10.
538. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA. 2008;299:532–9. Erratum in: JAMA. 2008;299:2390.
539. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555–62.
540. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008;358:1229–39.
541. Dangas G, Mehran R, Guagliumi G, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol. 2009;54:1438–46.
542. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA. 2003;289:853–63. Erratum in: JAMA. 2003;289:1638.
543. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA. 2005;294:3108–16. Erratum in: JAMA. 2006;295:628.
544. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006;114:774–82.
545. Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol. 2006;47:809–16.
546. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol. 2007;49:1362–8.
547. Mathews R, Peterson ED, Chen AY, et al. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry-GWTG. Am J Cardiol. 2011;107:1136–43.
548. Mehta SK, Frutkin AD, Lindsey JB, et al. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. Circ Cardiovasc Interv. 2009;2:222–9.
549. Kadakia MB, Desai NR, Alexander KP, et al. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry-GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry—Get With the Guidelines). JACC Cardiovasc Interv. 2010;3:1166–77.
550. Hochholzer W, Wiviott SD, Antman EM, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation. 2011;123:2681–9.
551. Hébert PC, Wells G, Blajchman MA, et al; Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340:409–17. Erratum in: N Engl J Med. 1999;340:1056.

552. Aronson D, Dann EJ, Bonstein L, et al. Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. Am J Cardiol. 2008;102:115–9.
553. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55:2556–66.
554. Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:257S--98S.
555. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358:2127–37.
556. Claassen DO, Kazemi N, Zubkov AY, et al. Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. Arch Neurol. 2008;65:1313–8.
557. Nikolsky E, Mehran R, Dangas G, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J. 2007;28:1936–45.
558. Rao SV, Ou F-S, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. JACC Cardiovasc Interv. 2008;1:379–86.
559. Agostoni P, Biondi-Zoccai GGL, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures: systematic overview and meta-analysis of randomized trials. J Am Coll Cardiol. 2004;44:349–56.
560. Chase AJ, Fretz EB, Warburton WP, et al. Association of the arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L study (Mortality benefit Of Reduced Transfusion after percutaneous coronary intervention via the Arm or Leg). Heart. 2008;94:1019–25.
561. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet. 2011;377:1409–20. Errata in: Lancet. 2011;377:1408 and Lancet. 2011;378:30.
562. Patel MR, Jneid H, Derdeyn CP, et al. Arteriotomy closure devices for cardiovascular procedures: a scientific statement from the American Heart Association. Circulation. 2010;122:1882–93. Erratum in: Circulation. 2010;122:e507.
563. Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. JAMA. 2010;303:2156–64.
564. Koreny M, Riedmüller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA. 2004;291:350–7.
565. Doyle BJ, Ting HH, Bell MR, et al. Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. JACC Cardiovasc Interv. 2008;1:202–9.
566. Dauerman HL, Rao SV, Resnic FS, et al. Bleeding avoidance strategies: consensus and controversy. J Am Coll Cardiol. 2011;58:1–10.
567. Kosiborod M, McGuire DK. Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. Circulation. 2010;122:2736–44.
568. Pinto DS, Skolnick AH, Kirtane AJ, et al. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2005;46:178–80.
569. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation. 2008;117:1018–27.
570. Finfer S, Chittock DR, Su SY-S, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
571. Mehta SR, Yusuf S, Díaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA. 2005;293:437–46.
572. van der Horst ICC, Zijlstra F, van 't Hof AWJ, et al. Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. J Am Coll Cardiol. 2003;42:784–91.
573. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA. 2012;307:1925–33.
574. Newby LK, Eisenstein EL, Califf RM, et al. Cost effectiveness of early discharge after uncomplicated acute myocardial infarction. N Engl J Med. 2000;342:749–55.
575. Newby LK, Hasselblad V, Armstrong PW, et al. Time-based risk assessment after myocardial infarction: implications for timing of discharge and applications to medical decision-making. Eur Heart J. 2003;24:182–9.
576. Antman EM, Kuntz KM. The length of the hospital stay after myocardial infarction. N Engl J Med. 2000;342:808–10.
577. Théroux P, Waters DD, Halphen C, et al. Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med. 1979;301:341–5.
578. Villella A, Maggioni AP, Villella M, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 data-base: Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto. Lancet. 1995;346:523–9.
579. Leppo JA, O'Brien J, Rothendler JA, et al. Dipyridamole-thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. N Engl J Med. 1984;310:1014–8.
580. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. Circulation. 2009;119:e561–87.
581. Douglas PS, Garcia MJ, Haines DE, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2011;57:1126–66.
582. Thomas RJ, King M, Lui K, et al. AACVPR/ACCF/AHA 2010 update: performance measures on cardiac rehabilitation for referral to cardiac rehabilitation/secondary prevention services. Circulation. 2010;122:1342–50.
583. Jain A, Myers GH, Sapin PM, et al. Comparison of symptom-limited and low level exercise tolerance tests early after myocardial infarction. J Am Coll Cardiol. 1993;22:1816–20.
584. Roffi M, Wenaweser P, Windecker S, et al. Early exercise after coronary stenting is safe. J Am Coll Cardiol. 2003;42:1569–73.
585. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2003;107:149–58. Erratum in: J Am Coll Cardiol. 2006;48:1731.
586. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation. 2003;108:1404–18.
587. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351:2481–8.
588. Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361:1427–36.
589. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877–83.
590. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37. Erratum in: N Engl J Med. 2005;352:2146.
591. Goldenberg I, Gillespie J, Moss AJ, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation. 2010;122:1265–71.

592. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2012;126:1784-1800. Erratum in: Circulation. 2013;127:e357–9.
593. Naylor M, Brooten D, Jones R, et al. Comprehensive discharge planning for the hospitalized elderly: a randomized clinical trial. Ann Intern Med. 1994;120:999–1006.
594. Coleman EA, Parry C, Chalmers S, et al. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med. 2006; 166:1822–8.
595. Young W, Rewa G, Goodman SG, et al. Evaluation of a community-based inner-city disease management program for postmyocardial infarction patients: a randomized controlled trial. CMAJ. 2003;169:905–10.
596. Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. Ann Intern Med. 2009;150:178–87.
597. Lappé JM, Muhlestein JB, Lappé DL, et al. Improvements in 1-year cardiovascular clinical outcomes associated with a hospital-based discharge medication program. Ann Intern Med. 2004;141:446–53.
598. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2005;111:369–76. Erratum in: Circulation. 2005;111:1717.
599. Suaya JA, Stason WB, Ades PA, et al. Cardiac rehabilitation and survival in older coronary patients. J Am Coll Cardiol. 2009;54:25–33.
600. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med. 2004;116:682–92.
601. Goel K, Lennon RJ, Tilbury RT, et al. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation. 2011;123:2344–52.
602. Wilson K, Gibson N, Willan A, et al. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med. 2000;160:939–44.
603. Thomson CC, Rigotti NA. Hospital- and clinic-based smoking cessation interventions for smokers with cardiovascular disease. Prog Cardiovasc Dis. 2003;45:459–79.
604. Dawood N, Vaccarino V, Reid KJ, et al. Predictors of smoking cessation after a myocardial infarction: the role of institutional smoking cessation programs in improving success. Arch Intern Med. 2008;168:1961–7.
605. Shah AM, Pfeffer MA, Hartley LH, et al. Risk of all-cause mortality, recurrent myocardial infarction, and heart failure hospitalization associated with smoking status following myocardial infarction with left ventricular dysfunction. Am J Cardiol. 2010;106:911–6.
606. Bernheim SM, Grady JN, Lin Z, et al. National patterns of risk-standardized mortality and readmission for acute myocardial infarction and heart failure: update on publicly reported outcomes measures based on the 2010 release. Circ Cardiovasc Qual Outcomes. 2010;3:459–67.
607. Coleman EA. Falling through the cracks: challenges and opportunities for improving transitional care for persons with continuous complex care needs. J Am Geriatr Soc. 2003;51:549–55.
608. Coleman EA, Boult C. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc. 2003;51:556–7.
609. Coleman EA, Mahoney E, Parry C. Assessing the quality of preparation for posthospital care from the patient's perspective: the care transitions measure. Med Care. 2005;43:246–55.
610. Bernheim SM, Spertus JA, Reid KJ, et al. Socioeconomic disparities in outcomes after acute myocardial infarction. Am Heart J. 2007;153:313–9.
611. Rahimi AR, Spertus JA, Reid KJ, et al. Financial barriers to health care and outcomes after acute myocardial infarction. JAMA. 2007;297:1063–72.
612. Smolderen KG, Spertus JA, Reid KJ, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. Circ Cardiovasc Qual Outcomes. 2009;2:328–37.
613. Kaiser Permanente. Case Study: Collaborative Cardiac Care Service—Collaborative Teams Improve Cardiac Care with Health Information Technology. March 27, 2009. Available at: http://xnet.kp.org/future/ahrstudy/032709cardiac.html. Accessed March 10, 2011.
614. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2007;115:2675–82.
615. Suaya JA, Shepard DS, Normand S-LT, et al. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. Circulation. 2007;116:1653–62.
616. Snow V, Beck D, Budnitz T, et al. Transitions of care consensus policy statement American College of Physicians-Society of General Internal Medicine-Society of Hospital Medicine-American Geriatrics Society-American College of Emergency Physicians-Society of Academic Emergency Medicine. J Gen Intern Med. 2009;24:971–6.
617. National Quality Forum. Safe Practices for Healthcare 2010 update. Available at: http://qualityforum.org/projects/safe_practices_2010.aspx. Accessed December 9, 2010.
618. The Joint Commission. 2010 National Patient Safety Goals. Available at: http://www.jointcommission.org/standards_information/npsgs.aspx. Accessed December 9, 2010.
619. National Quality Forum. Preferred practices and performance measures for measuring and reporting care coordination. Available at: http://qualityforum.org/projects/care_coordination.aspx. Accessed December 9, 2010.
620. Desai MM, Stauffer BD, Feringa HHH, et al. Statistical models and patient predictors of readmission for acute myocardial infarction: a systematic review. Circ Cardiovasc Qual Outcomes. 2009;2:500–7.
621. Verouden NJW, Haeck JDE, Kuijt WJ, et al. Prediction of 1-year mortality with different measures of ST-segment recovery in all-comers after primary percutaneous coronary intervention for acute myocardial infarction. Circ Cardiovasc Qual Outcomes. 2010;3:522–9.
622. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. November 20. doi:10.1161/CIR.0b013e318277d6a0. Available at: http://circ.ahajournals.org/lookup/doi/10/1161/CIR.0b013e318277d6a0. Accessed November 20, 2012.
623. American College of Chest Physicians. Tobacco Cessation Toolkit. Available at: http://tobaccodependence.chestnet.org/. Accessed March 9, 2011.
624. Deleted in press.
625. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560–72. Erratum in: JAMA. 2003;290:197.
626. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007;30:162–72.
627. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119:e391–479. Erratum in: Circulation. 2010;121:e258.

627a Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2012;125:1058–72

628. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation. 2004;109:672–93.
629. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation. 2008;118:1768–75.
630. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2005;54:1–40.

631. Curry LA, Spatz E, Cherlin E, et al. What distinguishes top-performing hospitals in acute myocardial infarction mortality rates? A qualitative study. Ann Intern Med. 2011;154:384–90.
632. Lambert L, Brown K, Segal E, et al. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. JAMA. 2010;303:2148–55.
633. STREAM (Strategic Reperfusion [With Tenecteplase and Antithrombotic Treatment] Early After Myocardial Infarction) Trial. 2011. ClinicalTrials.gov identifier: NCT00623623. Available at: http://clinicaltrials.gov/ct2/show/NCT00623623. Accessed November 1, 2010.
634. McLean S, Wild S, Connor P, et al. Treating ST elevation myocardial infarction by primary percutaneous coronary intervention, in-hospital thrombolysis and prehospital thrombolysis: an observational study of timelines and outcomes in 625 patients. Emerg Med J. 2011;28:230–6.
635. Blankenship JC, Scott TD, Skelding KA, et al. Door-to-balloon times under 90 min can be routinely achieved for patients transferred for ST-segment elevation myocardial infarction percutaneous coronary intervention in a rural setting. J Am Coll Cardiol. 2011;57:272–9.
636. Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Arch Intern Med. 2010;170:1842–9.
637. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet. 2010;376:1312–9.
638. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366:9–19.
639. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med. 2012;366:20–33.
640. Bekkers SCAM, Yazdani SK, Virmani R, et al. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. J Am Coll Cardiol. 2010;55:1649–60.
641. Timmers L, Henriques JPS, de Kleijn DPV, et al. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. J Am Coll Cardiol. 2009;53:501–10.
642. Wu KC. Fighting the "fire" of myocardial reperfusion injury: how to define success? J Am Coll Cardiol. 2009;53:730–1.
643. Deleted in press.
644. Prasad A, Stone GW, Holmes DR, et al. Reperfusion injury, microvascular dysfunction, and cardioprotection: the "dark side" of reperfusion. Circulation. 2009;120:2105–12.
645. Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation. 2011;123:1622–32.
646. Dorian P, Hohnloser SH, Thorpe KE, et al. Mechanisms underlying the lack of effect of implantable cardioverter-defibrillator therapy on mortality in high-risk patients with recent myocardial infarction: insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT). Circulation. 2010;122:2645–52.
647. Terzic A, Nelson TJ. Regenerative medicine advancing health care 2020. J Am Coll Cardiol. 2010;55:2254–7.
648. Schächinger V, Erbs S, Elsässer A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. 2006;355:1210–21.
649. Hirsch A, Nijveldt R, van der Vleuten PA, et al. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. Eur Heart J. 2011;32:1736–47.
650. Roncalli J, Mouquet F, Piot C, et al. Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial. Eur Heart J. 2011; 32:1748–57.
651. Traverse JH, Henry TD, Ellis SG, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. JAMA. 2011;306:2110–9.
652. Makkar RR, Smith RR, Cheng K, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet. 2012;379:895–904.
653. Ptaszek LM, Mansour M, Ruskin JN, et al. Towards regenerative therapy for cardiac disease. Lancet. 2012;379:933–42.
654. Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet. 2006;367:113–21.
655. Dill T, Schächinger V, Rolf A, et al. Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging substudy. Am Heart J. 2009;157:541–7.
656. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet. 2011;378:1847–57.

KEY WORDS: AHA Scientific Statements ■ anticoagulants ■ antiplatelets ■ door-to-balloon ■ fibrinolysis ■ percutaneous coronary intervention ■ reperfusion ■ ST-elevation myocardial infarction ■ thrombolysis

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Patrick T. O'Gara, Chair	Harvard Medical School—Professor of Medicine	None	None	None	None	None	None	None
Frederick G. Kushner, Vice Chair	Tulane University School of Medicine—Clinical Professor of Medicine; Heart Clinic of Louisiana—Medical Director	None	None	None	None	• Novartis†	None	8.1 8.2
Deborah D. Ascheim	Mount Sinai School of Medicine—Associate Professor; InCHOIR—Clinical Director of Research	None	None	None	None	None	None	None
Donald E. Casey, Jr.	Atlantic Health—Chief Medical Officer and Vice President of Quality	None	None	None	None	None	None	None
Mina K. Chung	Cleveland Clinic Foundation—Associate Professor of Medicine	• Biotronik† • Boston Scientific† • Nexcura † • PGx† • Sanofi-aventis† • St. Jude Medical†	None	None	• Biotronik† • Boston Scientific† • GlaxoSmithKline† • Medtronic† • Siemens Medical Solutions† • St. Jude Medical† • ZOLL†	• Medtronic† • Boston Scientific† • St. Jude Medical†	None	None
James A. de Lemos	UT Southwestern Medical School—Professor of Medicine	• Johnson & Johnson • Tethys • AstraZeneca • Daiichi-Sankyo	• BMS/ Sanofi-aventis	None	• Bristol-Myers Squibb (DSMB) • Roche • Merck/Schering-Plough • Daiichi-Sankyo	None	None	4.4.1 4.4.2 5.1.4.1 5.1.4.2 6.4.1 6.4.2 7.2 9.6
Steven M. Ettinger	Penn State Heart & Vascular Institute—Professor of Medicine and Radiology	None	None	None	• Medtronic§	None	None	4.3.1
James C. Fang	University Hospitals Case Medical Center—Director, Heart Transplantation	• Accorda • Novartis • Thoratec	None	None	None	• Medtronic	None	9.5.4.1
Francis M. Fesmire	Heart Stroke Center—Director	• Abbott	None	None	None	None	• Plaintiff, Missed ACS, 2010	8.3
Barry A. Franklin	William Beaumont Hospital—Director, Cardiac Rehabilitation and Exercise Laboratories	None	None	None	None	None	None	None
Christopher B. Granger	Duke Clinical Research Institute—Director, Cardiac Care Unit; Assistant Professor of Medicine	• AstraZeneca • Boehringer Ingelheim‡ • Bristol-Myers Squibb • GlaxoSmithKline • Hoffman La Roche • Novartis • Sanofi-aventis‡ • The Medicines Company	None	None	• Astellas • AstraZeneca • Boehringer Ingelheim‡ • Bristol-Myers Squibb • Eli Lilly • GlaxoSmithKline • Medtronic • Merck • Sanofi-aventis‡ • The Medicines Company	None	None	4.4.1 6.4.2 9.7.1

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Harlan M. Krumholz	Yale University School of Medicine—Professor of Medicine	• United HealthCare (Science Advisory Group)	None	None	None	None	None	None
Jane A. Linderbaum	Mayo Clinic—Assistant Professor of Medicine	None	None	None	None	None	None	None
David A. Morrow	Harvard Medical School—Associate Professor of Medicine	• Beckman-Coulter • Boehringer Ingelheim • Daiichi-Sankyo • Eli Lilly • Genentech • Merck • Novartis • OrthoClinical Diagnostics/Johnson & Johnson • Roche Diagnostics • Sanofi-aventis • Schering-Plough Research Institute • Siemens Medical Solutions	None	None	• AstraZeneca‡ • Beckman-Coulter‡ • Daiichi-Sankyo‡ • Eli Lilly‡ • GlaxoSmithKline‡ • Merck‡ • Nanosphere‡ • Novartis‡ • Roche Diagnostics‡ • Sanofi-aventis‡ • Schering-Plough Research Institute‡ • Siemens Medical Solutions‡ • Singulex‡	• AstraZeneca‡	None	3.2 4.4.1 4.4.2 5.1 5.1.4.1 6.4.1 6.4.2 7.2 8.2 8.3 9.6
L. Kristin Newby	Duke University Medical Center, Division of Cardiology—Professor of Medicine	• Amgen‡ • AstraZeneca • BioVascular • Johnson & Johnson • Novartis	None	None	• BG Medicine • Bristol-Myers Squibb • diaDexus‡ • Eli Lilly • GlaxoSmithKline‡ • Johnson & Johnson • Merck‡ • Regado • Schering-Plough‡	None	None	4.4.1 7.2
Joseph P. Ornato	Department of Emergency Medicine Virginia Commonwealth University—Professor and Chairman	• European Resuscitation Council‡ • ZOLL Circulation	None	None	• NIH/NINDS Neurological Emergency Treatment Trials Consortium—PI‡	None	None	None
Narith Ou	Mayo Clinic—Pharmacotherapy Coordinator, Cardiology	None	None	None	None	None	None	None
Martha J. Radford	NYU Langone Medical Center—Chief Quality Officer; NYU School of Medicine—Professor of Medicine (Cardiology)	None	None	None	None	None	None	None
Jacqueline E. Tamis-Holland	St Luke's-Roosevelt Hospital Center—Director, Interventional Cardiology Fellowship Program; Columbia University, College of Physicians and Surgeons—Assistant Professor of Clinical Medicine	None	None	None	None	None	None	None

(Continued)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Carl L. Tommaso	Skokie Hospital—Director of Catheterization Laboratory; North Shore University Health Systems	None	None	None	None	None	None	None
Cynthia M. Tracy	George Washington University Medical Center—Associate Director, Division of Cardiology	None	None	None	None	None	None	None
Y. Joseph Woo	Hospital of the University of Pennsylvania—Associate Professor of Surgery	None	None	None	None	None	None	None
David X. Zhao	Vanderbilt University Medical Center—Director, Cardiac Catheterization and Interventional Cardiology	None	None	None	• Abbot Vascular • Accumetrics • AGA Medical • Osiris • Volcano	None	None	4.3.1

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities could apply.

†No financial benefit.

‡Significant relationship.

§Dr. Ettinger's relationship with Medtronic was added just before balloting of the recommendations, so it was not relevant during the writing stage; however, the addition of this relationship makes the writing committee out of compliance with the minimum 50% no relevant RWI requirement.

ACS indicates acute coronary syndromes; DSMB, data safety monitoring board; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; and PI, principal investigator.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Elliott M. Antman	Official Reviewer—ACCF Board of Trustees	None	None	None	• Accumetrics • AstraZeneca • Beckman Coulter • Bristol-Myers Squibb Pharmaceutical Research Institute • Daiichi-Sankyo* • Eli Lilly* • GlaxoSmithKline • Merck • Millennium Pharmaceuticals • Novartis Pharmaceuticals • Ortho-Clinical Diagnostics • Sanofi-Synthelabo Recherche • Schering-Plough Research Institute	None	None
Gary J. Balady	Official Reviewer—AHA	None	None	None	None	None	None
Christopher P. Cannon	Official Reviewer—AHA	• Novartis†	None	None	• Accumetrics* • AstraZeneca* • Bristol-Myers Squibb† • GlaxoSmithKline • Merck*	• GlaxoSmithKline • Merck (DSMB)	None
Judith S. Hochman	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	• BMS/Sanofi • Eli Lilly • GlaxoSmithKline	None	None	None	• Johnson & Johnson Pharmaceutical Research & Development (DSMB) • Merck/Schering Plough (DSMB)	None
Austin H. Kutscher	Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Charles J. Davidson	Organizational Reviewer—SCAI	• Abbott* • Abbott Vascular	None	None	• Edwards Lifesciences*	None	None
Deborah B. Diercks	Organizational Reviewer—ACEP	• Abbott Cardiovascular • Daiichi-Sankyo	None	None	• Beckman Coulter† • Nanosphere†	None	None
Jonathan M. Tobis	Organizational Reviewer—SCAI	None	• AGA Medical • Boston Scientific	None	• AGA Medical*	None	None
Jeffrey L. Anderson	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	• Toshiba†	• AstraZeneca (DSMB)	Defendant, Postoperative Ablation Case, 2010
James C. Blankenship	Content Reviewer	None	None	None	• AstraZeneca† • Boston Scientific† • Novartis† • Schering-Plough†	None	None
Jeffrey J. Cavendish	Content Reviewer—ACCF Prevention of Cardiovascular Disease Committee	None	None	None	None	None	None
Harold L. Dauerman	Content Reviewer	None	None	None	None	None	None
John S. Douglas, Jr.	Content Reviewer	None	None	None	• Abbott† • Medtronic† • The Medicines Company†	None	None
Stephen G. Ellis	Content Reviewer	• Abbott Vascular • Boston Scientific†	None	None	None	None	None

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Joseph Fredi	Content Reviewer—ACCF Surgeons' Scientific Council	• AGA Medical†	None	None	None	None	None
Anthony Gershlick	Content Reviewer	• Abbott • AstraZeneca • Boehringer Ingelheim • Boston Scientific • Cordis • Eli Lilly • Medtronic	None	None	• Boehringer Ingelheim	None	None
Howard C. Herrmann	Content Reviewer	• AstraZeneca • Merck Sharpe and Dohme	None	None	• Accumetrics • Boston Scientific* • Edwards Lifesciences* • eValve • Medtronic* • St. Jude Medical • The Medicines Company*	None	None
James Bernard Hermiller	Content Reviewer—ACCF Interventional Scientific Council	• Abbott • Boston Scientific • St. Jude Medical	• Eli Lilly	None	None	None	None
Fred M. Kosumoto	Content Reviewer	None	None	None	None	None	None
Glenn Levine	Content Reviewer	None	None	None	None	None	None
Roxana Mehran	Content Reviewer	• Abbott Vascular • AstraZeneca • Ortho-McNeill	None	None	• BMS/Sanofi-aventis* • The Medicines Company*	None	None
M. Eugene Sherman	Content Reviewer—ACCF Board of Governors	None	Eli Lilly*	None	None	None	None
Daniel I. Simon	Content Reviewer	• Cordis/Johnson & Johnson • Daiichi-Sankyo • Eli Lilly • Medtronic • Sanofi-aventis • The Medicines Company	None	None	None	None	Defendant, DES Intellectual Property Case, 2010
Richard W. Smalling	Content Reviewer—ACCF Interventional Scientific Council	• AGA Medical	None	None	• AGA Medical* • Cordis* • eValve*	• AGA Medical • Cordis • eValve	None
William G. Stevenson	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
William A. Tansey III	Content Reviewer	None	None	None	None	None	None
David D. Waters	Content Reviewer	• Bristol-Myers Squibb • Pfizer	None	None	None	• Merck/Schering-Plough • Sanofi-aventis (DSMB)	None
Christopher J. White	Content Reviewer	None	None	None	• Boston Scientific† • St. Jude Medical	None	None

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Clyde W. Yancy	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Yerem Yeghiazarians	Content Reviewer	None	None	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Significant relationship.

†No financial benefit.

ACCF indicates American College of Cardiology Foundation; ACEP, American College of Emergency Physicians; AHA, American Heart Association; DES, drug-eluting stent; DSMB, data safety monitoring board; and SCAI, Society for Cardiovascular Angiography and Interventions.

Appendix 3. Abbreviation List

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
AF = atrial fibrillation
ARB = angiotensin receptor blocker
AV = atrioventricular
BMS = bare-metal stent
BP = blood pressure
CABG = coronary artery bypass graft
COX-2 = cyclooxygenase-II enzyme
CPR = cardiopulmonary resuscitation
CrCl = creatinine clearance
D2B = door-to-balloon (device)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
ECG = electrocardiogram/electrocardiographic
ED = emergency department
EF = ejection fraction
EMS = emergency medical services
FMC = first medical contact
GP = glycoprotein
HF = heart failure
HIT = heparin-induced thrombocytopenia
IABP = intra-aortic balloon counterpulsation
ICD = implantable cardioverter-defibrillator
ICH = intracranial hemorrhage
LBBB = left bundle-branch block
LDL = low-density lipoprotein
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NRMI = National Registry of Myocardial Infarction
PCI = percutaneous coronary intervention
RCT = randomized controlled trial
RV = right ventricular
SCD = sudden cardiac death
STEMI = ST-elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
UFH = unfractionated heparin
VF = ventricular fibrillation
VT = ventricular tachycardia