

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: Developed in Collaboration With the Canadian Cardiovascular Society Endorsed by the American Academy of Family Physicians : 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee

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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

*Developed in Collaboration With the Canadian Cardiovascular Society
Endorsed by the American Academy of Family Physicians*

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‡Recused from voting on Section 5: Facilitated PCI.

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§§Recused from voting on Section 13: Antiplatelet Therapy.

This document is a limited update to the 2004 guidelines update and is based on a review of certain evidence, not a full literature review.

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Preamble

A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data upon which recommendations are based. In an effort to respond more quickly to new evidence, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines has created a new “focused update” process to revise the existing guideline recommendations that are affected by evolving data or opinion. Before the initiation of this focused approach, periodic updates and revisions of existing guidelines required up to 3 years to

complete. Now, however, new evidence will be reviewed in an ongoing fashion to more efficiently respond to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence will be reviewed at least twice a year, and updates will be initiated on an as needed basis as quickly as possible, while maintaining the rigorous methodology that the ACC and AHA have developed during their more than 20 years of partnership.

These updated guideline recommendations reflect a consensus of expert opinion following a thorough review that consisted primarily of late-breaking clinical trials identified through a broad-based vetting process as important to the relevant patient population and of other new data deemed to have an impact on patient care (see Section 1.1 for details on this focused update). It is important to note that this focused update is not intended to represent an update based on a full literature review from the date of the previous guideline publication. Specific criteria/considerations for inclusion of new data include:

- Publication in a peer-reviewed journal
- Large, randomized, placebo-controlled trial(s)
- Nonrandomized data deemed important on the basis of results that impact current safety and efficacy assumptions
- Strengths/weakness of research methodology and findings
- Likelihood of additional studies influencing current findings
- Impact on current performance measure(s) and/or likelihood of the need to develop new performance measure(s)
- Requests and requirements for review and update from the practice community, key stakeholders, and other sources free of relationships with industry or other potential bias
- Number of previous trials showing consistent results
- Need for consistency with other guidelines or guideline revisions

In analyzing the data and developing updated recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the ACC/AHA Task Force on Practice Guidelines, which are described elsewhere.^{1,2}

The schema for class of recommendation and level of evidence is summarized in Table 1, which also illustrates how the grading system provides estimates of the size of the treatment effect and the certainty of the treatment effect. Note that a recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although randomized trials may not be available, there may be a very clear clinical consensus that a particular test or therapy is useful and effective. Both the class of recommen-

Table 1. Applying Classification of Recommendations and Level of Evidence†

| | | SIZE OF TREATMENT EFFECT → | | | |
|---|---|--|---|--|---|
| | | CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered | CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment | CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED | CLASS III <i>Risk ≥ Benefit</i> No additional studies needed Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL |
| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | LEVEL A Multiple (3-5) population risk strata evaluated* General consistency of direction and magnitude of effect | <ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> ■ 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 (2-3) population risk strata evaluated* | <ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Limited evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Limited evidence from single randomized trial or nonrandomized studies |
| | LEVEL C Very limited (1-2) population risk strata evaluated* | <ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard-of-care |
| Suggested phrases for writing recommendations† | | should is recommended is indicated is useful/effective/beneficial | is reasonable can be useful/effective/beneficial is probably recommended or indicated | may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established | is not recommended is not indicated should not is not useful/effective/beneficial may be harmful |

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

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

dation and level of evidence listed in the focused updates are based on consideration of the evidence reviewed in previous iterations of the guidelines as well as the focused update. Of note, the implications of older studies that have informed recommendations but have not been repeated in contemporary settings are carefully considered.

The ACC/AHA practice guidelines address patient populations (and health care providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and on the relevance to the ACC/AHA target

population to determine whether the findings should inform a specific recommendation.

The ACC/AHA practice guidelines are intended to assist health care providers in clinical decision making by describing a range of generally acceptable approaches for 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 health care provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availabil-

ity of expertise in the area where care is provided. These guidelines may be used as the basis for regulatory or payer decisions, but the ultimate goal is quality of care and serving the patient's best interests.

Prescribed courses of treatment in accordance with these recommendations are only effective if they are followed by the patient. Because lack of patient adherence may adversely affect treatment outcomes, health care providers should make every effort to engage the patient in active participation with prescribed treatment.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflict of interest arising from industry relationships or personal interests of a writing committee member. All writing committee members and peer reviewers were required to provide disclosure statements of all such relationships pertaining to the trials and other evidence under consideration (see Appendixes 1 and 2). Final recommendations were balloted to all writing committee members. Writing committee members with significant (greater than \$10 000) relevant relationships with industry (RWI) were required to recuse themselves from voting on that recommendation. Writing committee members who did not participate are not listed as authors of this focused update.

With the exception of the recommendations presented here, the full guidelines remain current. Only the recommendations from the affected section(s) of the full guidelines are included in this focused update. For easy reference, all recommendations from any section of guidelines impacted by a change are presented with a notation as to whether they remain current, are new, or have been modified. When evidence impacts recommendations in more than 1 set of guidelines, those guidelines are updated concurrently.

The recommendations in this focused update will be considered current until they are superseded by another focused update or the full-text guidelines are revised. This focused update is published in the January 15, 2008, issue of the *Journal of the American College of Cardiology* and the January 15, 2008, issue of *Circulation* as an update to the full-text guidelines and is also posted on the ACC (www.acc.org) and AHA (www.americanheart.org) Web sites. Copies of the focused update are available from both organizations.

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1. Introduction

1.1. Evidence Review

Late-breaking clinical trials presented at the 2005 and 2006 annual scientific meetings of the ACC, AHA, and European Society of Cardiology, as well as selected other data, were reviewed by the standing guideline writing committee along with the parent Task Force and other experts to identify those trials and other key data that might impact guidelines recommendations. On the basis of

the criteria/considerations noted above, recent trial data and other clinical information were considered important enough to prompt a focused update of the 2004 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction [see Chen ZM et al.³; Chen ZM et al.⁴; ASSENT-4 PCI⁵; Antman EM et al.⁶; Yusuf S et al.⁷; Bhatt DL et al.⁸; Sabatine MS et al.⁹; Bennett JS et al.¹⁰; Smith SC Jr et al.¹¹; OAT^{12,13} and TOSCA¹⁴].

When considering the new data for this focused update, the writing group faced the task of weighing evidence from studies enrolling large numbers of subjects outside North America. Although noting that practice patterns and the rigor applied to data collection, as well as the genetic makeup of subjects, might influence the observed magnitude of a treatment effect, the writing group believed the data were relevant to formulation of recommendations for management of ST-elevation myocardial infarction (STEMI) in North America. The reasons for this decision include that 1) a broad array of management strategies was represented, including substantial proportions of subjects who received some form of reperfusion therapy, 2) concomitant treatments with proven efficacy (e.g., aspirin, beta blockers, inhibitors of the renin-angiotensin-aldosterone system, and statins) were used in the majority of patients, and 3) it was considered an impractical expectation that the tens of thousands of patients with STEMI needed to meet the estimated sample size for contemporary clinical trials be enrolled exclusively at North American sites.

To provide clinicians with a comprehensive set of data, whenever possible the exact event rates in various treatment arms of clinical trials are presented to permit calculation of the absolute risk difference (ARD) and number needed to treat (NNT) or harm (NNH); the relative treatment effects are described either as odds ratio (OR), relative risk (RR), or hazard ratio (HR), depending on the format in the original publication.

Consult the full-text version or executive summary of the 2004 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction¹⁵ for policy on clinical areas not covered by the focused update. Individual recommendations updated in this focused update will be incorporated into future revisions and/or updates of the full-text guidelines.

1.2. Organization of Committee and Relationships With Industry

For this focused update, all members of the 2004 STEMI writing committee were invited to participate; those who agreed (referred to as the 2007 focused update writing group) were required to disclose all RWI relevant to the data under consideration.² Focused update writing group members who had no significant relevant RWI wrote the first draft of the focused update; the draft was then reviewed and revised by the full writing group. Each recommendation required a confidential vote by the writing group members before external review of the document. Any writing committee member with a significant

(greater than \$10 000) relationship with industry relevant to the recommendation was recused from voting on that recommendation.

1.3. Review and Approval

This document was reviewed by 3 outside reviewers nominated by the ACC and 3 outside reviewers nominated by the AHA, as well as 1 reviewer each from the American Academy of Family Physicians and the Canadian Cardiovascular Society (CCS) and 58 individual content reviewers. All reviewer RWI information was collected and distributed to the writing committee and is published in this document (see Appendix 2 for details).

This document was approved for publication by the governing bodies of the American College of Cardiology Foundation and the American Heart Association and endorsed by the American Academy of Family Physicians and the Canadian Cardiovascular Society.

2. Analgesia

Analysis of retrospective data¹⁶ has raised a question about the potentially adverse effects of morphine in patients with unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI). As a result, the recommendation for morphine pain relief has been reduced to a Class IIa recommendation for that patient population. Use of morphine remains a Class I recommendation for patients with STEMI, however, because STEMI patients should either have received reperfusion or are not candidates for reperfusion, and continuing pain requires relief in either case (Table 2).

Because of the known increased risk of cardiovascular events among patients taking cyclooxygenase-2 (COX-2) inhibitors and other nonsteroidal anti-inflammatory drugs (NSAIDs),^{17–19} these drugs should be discontinued immediately at the time of STEMI (see 2004 STEMI Guidelines, Section 7.12.5, for additional discussion).^{3,15,20,21} A substudy analysis from the ExTRACT TIMI-25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction

Treatment–Thrombolysis in Myocardial Infarction) trial²² demonstrated an increased risk of death, reinfarction, heart failure, or shock among patients who were taking NSAIDs within 7 days of enrollment. Longer-term management considerations and a discussion of the gradient of risk with the various NSAIDs are found in Section 7.12.5 of the 2004 STEMI Guidelines.¹⁵

3. Beta Blockers

The 2004 STEMI Guidelines recommendations (Table 3) were based on studies that showed a reduced incidence of subsequent reinfarction and recurrent ischemia in patients receiving both fibrinolytic therapy and intravenous (IV) beta blockers. However, uncertainty about the use of IV beta blockers in the setting of fibrinolytic therapy has increased following 2 later randomized trials of IV beta blockade,^{23,24} a post-hoc analysis of the use of atenolol in the GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) trial,²⁵ and a review of early beta-blocker therapy in myocardial infarction (MI)²⁶ that did not find significant reductions in mortality.¹⁵

3.1. COMMIT/CCS-2 (Metoprolol)

The COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) (4) randomized 45 852 patients within 24 hours of onset of suspected MI to receive metoprolol (up to 3 doses of 5 mg IV each in the first 15 minutes, followed by 200 mg orally daily) or matching placebo. Fifteen minutes after the IV doses, a 50-mg tablet of metoprolol or placebo was administered orally and repeated every 6 hours during Days 0 to 1 of hospitalization. From Day 2 onward, 200 mg of controlled-release metoprolol or placebo was administered orally daily (this is the Food and Drug Administration [FDA]-approved regimen for metoprolol in MI) until discharge from the hospital or up to a maximum of 4 weeks in hospital (in survivors, the mean was 15 days). The 2 prespecified co-primary outcomes were the composite of death, reinfarction,

Table 2. Updates to Section 6.3.1.3: Analgesia

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|---|--|
| | Class I | |
| Morphine sulfate (2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. (<i>Level of Evidence: C</i>) | 1. Morphine sulfate (2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. (<i>Level of Evidence: C</i>) | 2004 recommendation remains current in 2007 Update |
| | 2. Patients routinely taking NSAIDs (except for aspirin), both nonselective as well as COX-2 selective agents, before STEMI should have those agents discontinued at the time of presentation with STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use. (<i>Level of Evidence: C</i>) | |
| | Class III | |
| | 1. NSAIDs (except for aspirin), both nonselective as well as COX-2 selective agents, should not be administered during hospitalization for STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use. (<i>Level of Evidence: C</i>) | New recommendation |

COX-2 indicates cyclooxygenase-2; IV, intravenous/intravenously; NSAIDs, nonsteroidal anti-inflammatory drugs; and STEMI, ST-elevation myocardial infarction.

Table 3. Updates to Section 6.3.1.5: Beta Blockers

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|---|--|--|
| Class I | | |
| Oral beta-blocker therapy should be administered promptly to those patients without a contraindication, irrespective of concomitant fibrinolytic therapy or performance of primary PCI. (<i>Level of Evidence: A</i>) | 1. Oral beta-blocker therapy should be initiated in the first 24 hours for patients who do not have any of the following: 1) signs of heart failure, 2) evidence of a low output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). (<i>Level of Evidence: B</i>) | Modified recommendation (changed LOE and text) |
| Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for beta-blocker therapy as secondary prevention. (<i>Level of Evidence: C</i>) | 2. Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for beta-blocker therapy as secondary prevention. (<i>Level of Evidence: C</i>) | 2004 recommendation remains current in 2007 Update |
| Patients with moderate or severe LV failure should receive beta-blocker therapy as secondary prevention with a gradual titration scheme. (<i>Level of Evidence: B</i>) | 3. Patients with moderate or severe LV failure should receive beta-blocker therapy as secondary prevention with a gradual titration scheme. (<i>Level of Evidence: B</i>) | 2004 recommendation remains current in 2007 Update |
| Class IIa | | |
| It is reasonable to administer IV beta blockers promptly to STEMI patients without contraindications, especially if a tachyarrhythmia or hypertension is present. (<i>Level of Evidence: B</i>) | 1. It is reasonable to administer an IV beta blocker at the time of presentation to STEMI patients who are hypertensive and who do not have any of the following: 1) signs of heart failure, 2) evidence of a low output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). (<i>Level of Evidence: B</i>) | Modified recommendation (changed text) |
| Class III | | |
| | 1. IV beta blockers should not be administered to STEMI patients who have any of the following: 1) signs of heart failure, 2) evidence of a low output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). (<i>Level of Evidence: A</i>) | New recommendation |

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

IV indicates intravenous; LOE, level of evidence; LV, left ventricular; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

or cardiac arrest and death from any cause during the scheduled treatment period.

Neither of the co-primary study end points was significantly reduced by allocation to metoprolol. For every 1000 patients treated, allocation to metoprolol was associated with 5 fewer episodes of reinfarction, 5 fewer episodes of ventricular defibrillation, but 11 more episodes of cardiogenic shock. The excess of cardiogenic shock was seen chiefly from Days 0 to 1 after hospitalization, whereas the reductions in reinfarction and ventricular fibrillation appeared from Day 2 onward.

Allocation to metoprolol produced an average relative increase in cardiogenic shock of 30%, with higher rates for those greater than 70 years of age, or with systolic blood pressure less than 120 mm Hg, or with presenting heart rate greater than 110 bpm, or with Killip class greater than 1. On average across the whole study population, the absolute reduction in arrhythmia-related deaths and the absolute increase in cardiogenic shock-related deaths were of similar magnitude. No apparent difference was noted between the 2 treatment groups in the other attributed causes of death, either individually or in aggregate. Metoprolol allocation was associated with significantly more persistent hypotension and more cases of bradycardia.

Though patients at high or low risk could be identified, the authors noted that they were not able to identify any subgroups in which the benefits clearly outweighed the risks.

3.2. Conclusion

This focused update expands on the concepts introduced in the 2004 STEMI Guidelines, underscoring the potential risk of administering IV beta blockers to patients with severe heart failure or cardiogenic shock. There are several circumstances in which it can be useful (Class IIa) to administer an IV beta blocker acutely to a STEMI patient (Table 3), and these situations are discussed below. It is reasonable to administer IV beta-blocker therapy on Days 0 to 1 of hospitalization for STEMI when hypertension is present and the patient is not at an increased risk of cardiogenic shock on the basis of the risk factors defined above. Patients with sinus tachycardia or atrial fibrillation should have left ventricular (LV) function rapidly evaluated before administration of IV beta blockers (or other negative inotropes, such as non-dihydropyridine calcium channel blockers). From Day 2 onward, when beneficial effects on reinfarction and ventricular fibrillation are seen, administration of 200 mg of controlled-release oral metoprolol daily appears to be safe in hemodynamically stable patients with STEMI who are free of contraindications. It is prudent to initiate a dose of 50 mg of metoprolol orally every 6 hours, transitioning to a dose equivalent to 200 mg per day orally or the maximum tolerated dose. It should be noted that long-term use of oral beta blockers is strongly recommended (Class I, Level of Evidence: A) for second-

ary prevention in patients at highest risk, such as those with low ejection fraction, heart failure, or postshock, once they have stabilized, with gradual dose titration²⁷ (see the 2004 STEMI Guidelines, Sections 7.4.1 and 7.12.7).¹⁵

The results of the COMMIT-CCS 2 trial raise questions about the safety of early use of IV beta blockers, particularly in high-risk populations, and led the writing group to reexamine the overall evidence base for beta-blocker therapy. The evidence base for this therapy was developed more than 25 years ago in a treatment environment that differs from contemporary practice. Moreover, no study included an oral beta blocker–only arm. The writing group consensus, however, was not to change the classification of the current early oral beta-blocker recommendation but to restrict it to patients who are not at high risk for complications. In addition, because of the absence of a study that specifically evaluated oral therapy alone, the Level of Evidence has been changed from A to B. Nevertheless, early (within 24 hours) oral beta-blocker therapy remains a Class I recommendation for those patients who are not at high risk for complications. Whether this change should affect current performance measures is beyond the scope of this document. The findings of potential risk of beta-blocker therapy in COMMIT emphasize the importance of continually monitoring these patients throughout hospitalization for signs and symptoms of complications of therapy, as noted in other sections of the original guidelines (Sections 6.3.1.5, 7.4.1, and 7.12.7). Because of the uncertainty about the benefit of oral beta blockers early on (e.g., in COMMIT-CCS 2, Days 0 to 1), the writing group recommends further research and additional examination at the time of the next revision to the STEMI Guidelines.

4. Reperfusion

4.1. Logistics of Care

Regardless of the mode of reperfusion, the overarching concept is to minimize total ischemic time, which is defined as the time from onset of symptoms of STEMI to initiation of reperfusion therapy. It is increasingly clear that 2 types of hospital systems provide reperfusion therapy: those with percutaneous coronary intervention (PCI) capability and those without PCI capability. When PCI capability is available, the best outcomes are achieved by offering this strategy 24 hours per day, 7 days per week.²⁸ The systems goal should

be a first medical contact–to–balloon time within 90 minutes (Table 4, Figure 1). There should be an ongoing program of outcomes analysis and periodic case review to identify process-of-care strategies that will continually improve time to treatment and facilitate rapid and appropriate treatment. A comprehensive effort in this regard is the AHA Mission Lifeline program, a community-based national initiative to improve the quality of care and outcomes of patients with STEMI by improving health care system readiness and response to STEMI.²⁹ The “Door-to-Balloon (D2B): An Alliance for Quality” campaign (www.d2balliance.org), launched by the ACC in collaboration with many organizations, including the AHA, aims to improve the timeliness of primary PCI. The goal is to increase the percentage of patients who receive timely primary PCI, with an emphasis on having at least 75% of patients treated within 90 minutes of presentation at the hospital, with a recommendation for the use of evidence-based strategies to reduce needless delays.³⁰ The 75% goal was set in recognition that some patients have clinically relevant non–system-based delays that do not represent quality-of-care issues. In hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when the expected door-to-balloon time is within 90 minutes of first medical contact.^{31,32}

It is important to note that the door-to-balloon goal is a systems goal that may not be possible to achieve for an individual patient because of patient variables (uncertainty about diagnosis, evaluation and treatment of other life-threatening conditions, obtaining informed consent, etc.) that delay the patient’s arrival in the interventional cardiology laboratory or anatomical challenges (issues of arterial, coronary, or lesion access) that prolong the PCI procedure. In the absence of such circumstances, however, reperfusion should be achieved as soon as possible within this time, and many hospitals with refined systems are approaching median door-to-balloon times of 60 to 70 minutes. Discussions about measurement, particularly with respect to inclusion criteria and the appropriate time to end measurement, are beyond the scope of this document and are being considered by groups that are focusing on how to improve the alignment between what is measured and patient outcomes. The focus on measurement should not displace the emphasis on improving processes that will facilitate more rapid treatment that is delivered safely and appropriately. **This committee continues to endorse the**

Table 4. Updates to Section 6.3.1.6: Reperfusion

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|--|--|
| | Class I | |
| Primary PCI should be performed as quickly as possible with the goal of a medical contact–to–balloon or door-to-balloon interval of within 90 minutes. (<i>Level of Evidence: B</i>) | 1. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact (see Figure 1) as a systems goal. (<i>Level of Evidence: A</i>) | Modified recommendation (changed LOE and text) |
| STEMI patients presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolytic therapy unless contraindicated. (<i>Level of Evidence: A</i>) | 2. STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact (see Figure 1) should be treated with fibrinolytic therapy within 30 minutes of hospital presentation as a systems goal unless fibrinolytic therapy is contraindicated. (<i>Level of Evidence: B</i>) | Modified recommendation (changed LOE and text) |

PCI indicates primary coronary intervention; LOE, level of evidence; and STEMI, ST-elevation myocardial infarction.

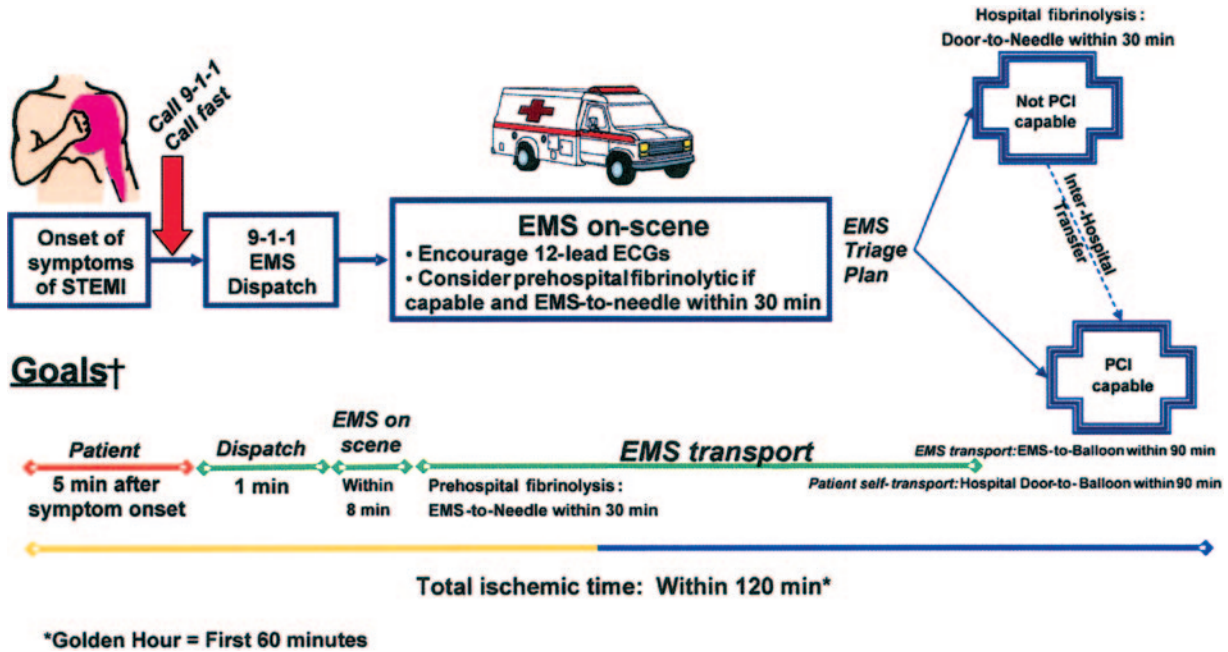


Figure 1. Options for Transportation of STEMI Patients and Initial Reperfusion Treatment Goals

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

Medical System Goals: EMS Transport (Recommended):

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

Patient Self-Transport (Discouraged):

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

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

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

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

Modified with permission.^{15,90}

concept that faster times to reperfusion and better systems of care are associated with important reductions in morbidity and mortality rates in patients with STEMI. An underutilized but effective strategy for improving systems of care for STEMI patients is to expand the use of prehospital 12-lead electrocardiography programs by emergency medical systems (EMS) that provide advanced life support.^{33,34}

The emphasis on primary PCI should not obscure the importance of fibrinolytic therapy. Many hospital systems in

North America do not have the capability of meeting the time goal for primary PCI.³⁵ Therefore, because of the critical importance of time to treatment from onset of symptoms of STEMI in reducing morbidity and mortality, fibrinolytic therapy is preferred. In these settings, transfer protocols need to be in place for arranging rescue PCI when clinically indicated.³⁶

For fibrinolytic therapy, the system goal is to deliver the drug within 30 minutes of the time that the patient presents to the hospital (Table 4). The focus for primary PCI is from first

medical contact because in regionalization strategies, extra time may be taken to transport patients to a center that performs the procedure. Consequently, it is important to consider the time from first medical contact. The writing group does believe that every effort should be made to reduce the time from first medical contact to fibrinolytic therapy when that is considered the appropriate reperfusion strategy.

5. Facilitated PCI

Facilitated PCI refers to a strategy of planned immediate PCI after administration of an initial pharmacological regimen intended to improve coronary patency before the procedure. These regimens have included high-dose heparin, platelet glycoprotein (GP) IIb/IIIa inhibitors, full-dose or reduced-dose fibrinolytic therapy, and the combination of a GP IIb/IIIa inhibitor with a reduced-dose fibrinolytic agent (e.g., fibrinolytic dose typically reduced 50%). Facilitated PCI should be differentiated from primary PCI without fibrinolytic therapy, from primary PCI with a GP IIb/IIIa inhibitor started at the time of PCI, from early or delayed PCI after successful fibrinolytic therapy, and from rescue PCI after unsuccessful fibrinolytic therapy. Potential advantages of facilitated PCI include earlier time to reperfusion, smaller infarct size, improved patient stability, lower infarct artery thrombus burden, greater procedural success rates, higher TIMI (Thrombolysis in Myocardial Infarction trial) flow rates, and improved survival rates. Potential risks include increased bleeding complications, especially in older patients. Potential limitations include additional cost.³⁷

Despite the potential advantages, clinical trials of facilitated PCI have not demonstrated any benefit in reducing infarct size or improving outcomes. The largest of these was the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial,⁵ in which 1667 patients were randomized to receive full-dose tenecteplase and PCI versus primary PCI. The trial was terminated prematurely because of a higher in-hospital mortality rate in the facilitated PCI group (6% vs. 3%; $p=0.01$). The primary end point, a composite of death, shock, and congestive heart failure within 90 days, was significantly higher with facilitated PCI than with primary PCI (18.6% vs. 13.4%; $p=0.0045$), and there was a trend toward a higher 90-day mortality rate (6.7% vs. 4.9%;

$p=0.14$). Defenders of the facilitated PCI strategy point out that the absence of an infusion of heparin after bolus administration and the absence of a loading dose of clopidogrel, plus prohibition of GP IIb/IIIa inhibitors except in bail-out situations, made adjunctive antithrombotic therapy suboptimal for the facilitated PCI group. Moreover, the median treatment delay between administration of tenecteplase and PCI was only 104 minutes, and mortality rates were higher in PCI centers. The evidence on whether earlier (prehospital) administration of fibrinolytic therapy, better antithrombotic therapy, longer delays to PCI, or selective use of PCI as a rescue strategy would make the facilitated PCI strategy beneficial is unclear. These issues require further study. On the basis of these data, however, facilitated PCI offered no clinical benefit.

Keeley and coworkers performed a quantitative review of 17 trials that compared facilitated PCI with primary PCI³⁸ (Figure 2). Nine trials involved GP IIb/IIIa inhibitors alone ($n=1148$), 6 trials with fibrinolytic therapy (including ASSENT-4 PCI) ($n=2953$), and 2 trials with a fibrinolytic agent plus a GP IIb/IIIa inhibitor ($n=399$). Facilitated PCI with fibrinolytic therapy had significantly higher rates of mortality, nonfatal reinfarction, urgent target-vessel revascularization, total and hemorrhagic stroke, and major bleeding compared with primary PCI. There were no differences in efficacy or safety when facilitated PCI with a GP IIb/IIIa inhibitor was compared with primary PCI.

A planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI may be harmful (Table 5). Nevertheless, selective use of the facilitated strategy with regimens other than full-dose fibrinolytic therapy in subgroups of patients at high risk (large MI or hemodynamic or electrical instability) with low risk of bleeding who present to hospitals without PCI capability might be performed when transfer delays for primary PCI are anticipated. Although quantitative analysis showed no advantage for pretreatment with a GP IIb/IIIa inhibitor, it did not document any major disadvantage either. The use of GP IIb/IIIa inhibitors, particularly abciximab, during primary PCI is well established.⁵⁵ Further trials of reduced-dose fibrinolytic therapy, with or without GP IIb/IIIa inhibitors, are in progress and may yield different efficacy and/or safety results.

Table 5. Updates to Section 6.3.1.6.4.4: Facilitated PCI

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|---|---|--|
| | Class IIb | |
| Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low. (Level of Evidence: B) | 1. Facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered as a reperfusion strategy when all of the following are present: a. Patients are at high risk, b. PCI is not immediately available within 90 minutes, and c. Bleeding risk is low (younger age, absence of poorly controlled hypertension, normal body weight). (Level of Evidence: C) | Modified recommendation (changed LOE and text) |
| | Class III | |
| | 1. A planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI may be harmful. (Level of Evidence: B) | New recommendation |

LOE indicates level of evidence; PCI, percutaneous coronary intervention, and STEMI, ST-elevation myocardial infarction.

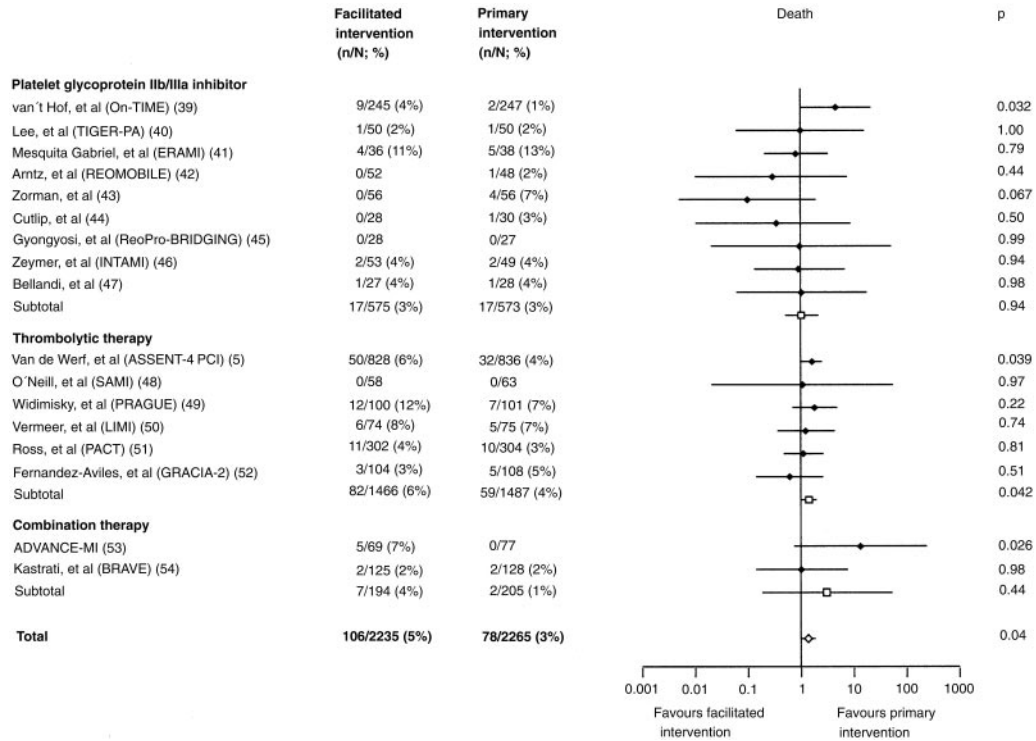


Figure 2. Short-Term Death in Patients Treated With Facilitated or Primary PCI. Trials were classified by facilitated regimen. Diamonds and squares indicate odds ratios. Lines indicate 95% confidence intervals. Reprinted with permission.³⁸

6. Immediate or Emergency Invasive Strategy and Rescue PCI

Pharmacological reperfusion with full-dose fibrinolysis is not uniformly successful in restoring antegrade flow in the infarct artery. In such situations, a strategy of prompt coronary angiography with intent to perform PCI is frequently contemplated. In certain patients, such as those with cardiogenic shock (especially those less than 75 years of age), severe congestive heart failure/pulmonary edema, or hemodynamically compromising ventricular arrhythmias (regardless of age), a strategy of coronary angiography with intent to perform PCI is a useful approach regardless of the time since initiation of fibrinolytic therapy, provided further invasive management is not considered futile or unsuitable given the clinical circumstances (Table 6). Further discussion of the management of such patients may be found in the 2004 STEMI Guidelines (see Section 6.3.1.6.4.6, as well as Sections 7.6.3 through 7.6.6).¹⁵ These sections have not been updated in this document.

In other patients who do not exhibit the clinical instability noted above, PCI may also be reasonable if there is clinical suspicion of failure of fibrinolysis. This is referred to as rescue PCI. Critical to the success of rescue PCI is the initial clinical identification of patients who are suspected of having failed reperfusion with full-dose fibrinolysis. Because the presence or absence of ischemic discomfort may be unreliable for identifying failed reperfusion, clinicians should search for evidence of inadequate ST-segment resolution on the 12-lead electrocardiogram (ECG). Operationally, the

12-lead ECG should be scrutinized after adequate time has elapsed before it is decided that fibrinolytic therapy has not been effective. Although earlier times have been used in some studies, the writing committee believed that 90 minutes after initiation of fibrinolysis was the best time point for evaluating the need for rescue PCI; hence, if there is less than 50% ST resolution in the lead showing the greatest degree of ST-segment elevation at presentation, fibrinolytic therapy has likely failed to produce reperfusion.

The 2004 STEMI Guidelines recommendations for rescue PCI were based on observational data and the results of 2 small randomized clinical trials (n=179) from the early 1990s.^{56,57} More recently, MERLIN (Middlesbrough Early Revascularization to Limit INfarction) (n=307), REACT (Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis) (n=427), and 3 meta-analyses have refocused attention on rescue PCI.⁵⁸⁻⁶² This subject has been studied with fewer than 1000 patients enrolled in randomized trials.

In the period between trials studying rescue PCI, there was a transition between angiographic and electrocardiographic diagnosis to detect failed reperfusion. Importantly, in the earlier studies, rescue PCI was performed in infarct arteries with TIMI 0/1 flow, often after a protocol-mandated 90-minute angiogram. In MERLIN and REACT, however, patients were randomized if they had less than 50% ST-segment elevation resolution at 60 or 90 minutes, respectively. Many patients had patent infarct arteries on angiography; only 54% of patients in MERLIN and 74% of patients in REACT (which required less than TIMI grade 3 flow for PCI) actually underwent PCI. From a procedural standpoint, stents have

Table 6. Updates to Section 6.3.1.6.4.5: Immediate (or Emergency) Invasive Strategy and Rescue PCI

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|---|--|
| Class I | | |
| Rescue PCI should be performed in patients less than 75 years old with ST elevation or left bundle-branch block who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (<i>Level of Evidence: B</i>) | 1. A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is recommended for patients who have received fibrinolytic therapy and have any of the following: <ol style="list-style-type: none"> a. Cardiogenic shock in patients less than 75 years who are suitable candidates for revascularization (<i>Level of Evidence: B</i>) b. Severe congestive heart failure and/or pulmonary edema (Killip class III) (<i>Level of Evidence: B</i>) c. Hemodynamically compromising ventricular arrhythmias (<i>Level of Evidence: C</i>) | Modified recommendation (changed LOE and text) |
| Class IIa | | |
| Rescue PCI is reasonable for selected patients 75 years or older with ST elevation or left bundle-branch block or who develop shock within 36 hours of MI and who are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and who agree to invasive care may be selected for such an invasive strategy. (<i>Level of Evidence: B</i>) | 1. A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is reasonable in patients 75 years of age or older who have received fibrinolytic therapy, and are in cardiogenic shock, provided that they are suitable candidates for revascularization. (<i>Level of Evidence: B</i>) | Modified recommendation (changed text) |
| It is reasonable to perform rescue PCI for patients with 1 or more of the following: <ol style="list-style-type: none"> a. Hemodynamic or electrical instability. (<i>Level of Evidence: C</i>) b. Persistent ischemic symptoms. (<i>Level of Evidence: C</i>) | 2. It is reasonable to perform rescue PCI for patients with 1 or more of the following: <ol style="list-style-type: none"> a. Hemodynamic or electrical instability. (<i>Level of Evidence: C</i>) b. Persistent ischemic symptoms. (<i>Level of Evidence: C</i>) | 2004 recommendation remains current in 2007 Update |
| | 3. A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation less than 50% resolved after 90 minutes following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and a moderate or large area of myocardium at risk (anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression). (<i>Level of Evidence: B</i>) | New recommendation |
| Class IIb | | |
| Rescue PCI in the absence of 1 or more of the above Class I or IIa indications is not recommended. (<i>Level of Evidence: C</i>) | 1. A strategy of coronary angiography with intent to perform PCI in the absence of one or more of the above Class I or IIa indications might be reasonable in moderate- and high-risk patients, but its benefits and risks are not well established. The benefits of rescue PCI are greater the earlier it is initiated after the onset of ischemic discomfort. (<i>Level of Evidence: C</i>) | Modified recommendation (changed COR from III to IIb and changed text) |
| Class III | | |
| | 1. A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is not recommended in patients who have received fibrinolytic therapy if further invasive management is contraindicated or the patient or designee does not wish further invasive care. (<i>Level of Evidence: C</i>) | New recommendation |

CABG indicates coronary artery bypass graft; COR, class of recommendation; LOE, level of evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

replaced balloon angioplasty, antiplatelet therapy has improved with the addition of a thienopyridine agent and often a GP IIb/IIIa receptor antagonist, and procedural success rates are higher.

Despite these historical differences, recent data support the initial observation that rescue PCI decreases adverse clinical events compared with medical therapy. In the Wijeyesundera meta-analysis⁶² (Figure 3), there was a trend toward reduced mortality rates with rescue PCI from 10.4% to 7.3% (RR 0.69 [95% confidence interval (CI) 0.46 to 1.05]; $p=0.09$), reduced reinfarction rates from 10.7% to 6.1% (RR 0.58 [95% CI 0.35 to 0.97]; $p=0.04$), and reduced heart failure rates from 17.8% to 12.7% (RR 0.73 [95% CI 0.54 to 1.00]; $p=0.05$). These event rates suggest that high-risk patients were selected for enrollment, so these data do not inform the

clinical community about the role of rescue PCI in lower-risk patients. Also, the benefits of rescue PCI need to be balanced against the risk. There was an excess occurrence of stroke in 2 trials (10 events vs. 2 events), but the majority of the strokes were thromboembolic rather than hemorrhagic, and the sample size was small, so more data are needed to define this risk. There also was an increase in absolute risk of bleeding of 13%, suggesting that adjustments in antithrombotic medication dosing are needed to improve safety. It should be noted that the majority of patients who underwent rescue PCI received fibrinolytic therapy with streptokinase.

Given the association between bleeding events and subsequent ischemic events,⁶³ it might be reasonable to select moderate- and high-risk patients for PCI after fibrinolysis and to treat low-risk patients with medical therapy. As noted above,

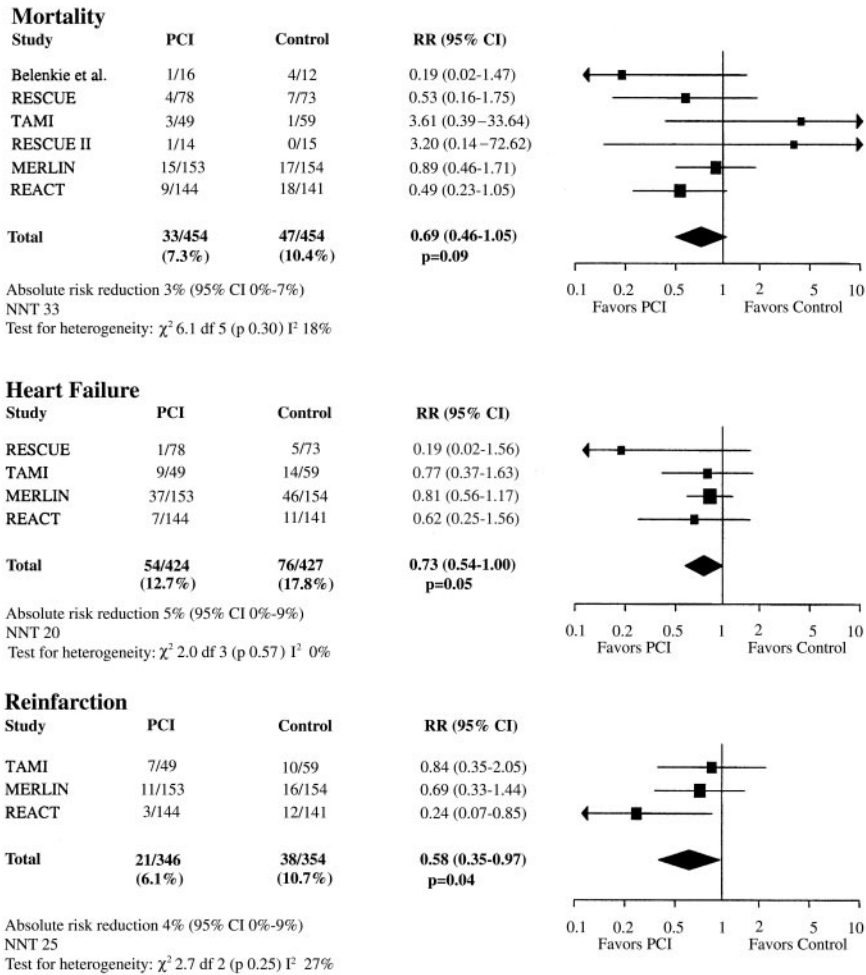


Figure 3. Efficacy End Points for Rescue PCI Versus Conservative Therapy. CI indicates confidence interval; MERLIN, Middlesbrough Early Revascularization to Limit Infarction trial; NNT, number needed to treat; PCI, percutaneous coronary intervention; REACT, Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis trial; RESCUE, Randomized Comparison of Rescue Angioplasty with Conservative Management of Patients with Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction trial; RR, relative risk; and TAMI, Thrombolysis and Angioplasty in Myocardial Infarction study. Reprinted with permission.⁶²

patients with cardiogenic shock, severe heart failure, or hemodynamically compromising ventricular arrhythmias are excellent candidates. An ECG estimate of potential infarct size in patients with persistent ST-segment elevation (less than 50% resolution at 90 minutes following initiation of fibrinolytic therapy in the lead showing the worst initial evaluation) and ongoing ischemic pain is useful for selecting other patients for rescue PCI. Anterior MI or inferior MI with right ventricular involvement or precordial ST-segment depression usually predicts increased risk.⁶⁴ Conversely, patients with symptom resolution, improving ST-segment elevation (less than 50% resolution), or inferior MI localized to 3 ECG leads probably should not be referred for angiography. Likewise, it is doubtful that PCI of a branch artery (diagonal or obtuse marginal branch) will change prognosis in the absence of high-risk criteria noted above.

7. PCI After Fibrinolysis or for Patients Not Undergoing Primary Reperfusion

As described in the 2004 STEMI Guidelines, PCI has been performed immediately after successful fibrinolytic therapy,

hours to days after successful fibrinolytic therapy, and days to weeks after successful fibrinolytic therapy.¹⁵ With the increase in use of an invasive strategy, consideration is now also given to PCI in patients who did not undergo fibrinolysis, and this concept is reflected in the decision of the writing committee to rename this section to reflect considerations for PCI both after fibrinolytic therapy and in STEMI patients who do not undergo primary reperfusion. See the 2004 STEMI Guidelines, Section 6.3.1.6, and updates herein to Sections 6.3.1.6.4.4 and 6.3.1.6.4.5 for additional discussions bearing on PCI after fibrinolysis.

7.1. The Late Open Artery Hypothesis: Clinical Outcomes

The open artery hypothesis suggested that late patency of an infarct artery is associated with improved LV function, increased electrical stability, and provision of collateral vessels to other coronary beds for protection against future events. The OAT (Occluded Artery Trial)^{12,13} tested the hypothesis that routine PCI for total occlusion 3 to 28 days after MI would reduce the composite of death, reinfarction, or

Table 7. Updates to Section 6.3.1.6.4.7: PCI After Successful Fibrinolysis or for Patients Not Undergoing Primary Reperfusion

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|---|--|--|
| Class IIb | | |
| Routine PCI might be considered as part of an invasive strategy after fibrinolytic therapy. (<i>Level of Evidence: B</i>) | 1. PCI of a hemodynamically significant stenosis in a patent infarct artery greater than 24 hours after STEMI may be considered as part of an invasive strategy. (<i>Level of Evidence: B</i>) | Modified recommendation (changed text) |
| Class III | | |
| | 1. PCI of a totally occluded infarct artery greater than 24 hours after STEMI is not recommended in asymptomatic patients with one- or two-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia. (<i>Level of Evidence: B</i>) | New recommendation |

PCI indicates percutaneous coronary intervention, and STEMI, ST-elevation myocardial infarction.

Class IV heart failure. Stable patients (n=2166) with an occluded infarct artery after MI (about 20% of whom received fibrinolytic therapy for the index event) were randomized to optimal medical therapy and PCI with stenting or optimal medical therapy alone. The qualifying period of 3 to 28 days was based on calendar days; thus, the minimal time from symptom onset to angiography was just over 24 hours. Inclusion criteria included total occlusion of the infarct-related artery with TIMI grade 0 or 1 antegrade flow and left ventricular ejection fraction (LVEF) less than 50% or proximal occlusion of a major epicardial artery with a large risk region. Exclusion criteria included NYHA Class III or IV heart failure, rest angina, serum creatinine greater than 2.5 mg per dL, left main or 3-vessel disease, clinical instability, or severe inducible ischemia on stress testing if the infarct zone was not akinetic or dyskinetic.¹² The 4-year cumulative end point was 17.2% in the PCI group and 15.6% in the medical therapy group (HR 1.16 [95% CI 0.92 to 1.45]; p=0.2).¹³ Reinfarction rates tended to be higher in the PCI group, which may have attenuated any benefit in LV remodeling. There was no interaction between treatment effect and any subgroup variable.

7.2. The Late Open Artery Hypothesis: Angiographic Outcomes

Preclinical studies have suggested that late opening of an occluded infarct artery may reduce adverse LV remodeling and preserve LV volumes. However, 5 previous clinical studies in 363 patients have demonstrated inconsistent improvement in LVEF or LV end-systolic and end-diastolic volumes after PCI. The largest of these, the DECOPI (DEsobstruction COronaire en Post-Infarctus) trial, found a higher LVEF at 6 months with PCI.⁶⁵ TOSCA-2 (Total Occlusion Study of Canada)¹⁴ enrolled 381 stable patients in a mechanistic ancillary study of OAT and had the same eligibility criteria.^{12,13} The PCI procedure success rate was 92% and the complication rate was 3%, although 9% had periprocedural MI as measured by cardiac biomarkers. At 1 year, patency rates (n=332) were higher with PCI (83% vs. 25%; p less than 0.0001), but each group (n=286) had equivalent improvement in LVEF (4.2% vs. 3.5%; p=0.47). There was modest benefit of PCI in preventing LV dilation over 1 year in a multivariate model, but only 42% had paired volume determinations, so it is unclear whether this finding extends to the whole cohort. The potential benefit of PCI in

attenuating remodeling may have been decreased by periprocedural MI and the high rate of beta blocker and angiotensin-converting enzyme (ACE) inhibitor use. There was no significant interaction between treatment effect and time, infarct artery, or infarct size.

7.3. Conclusion

These studies demonstrate that elective PCI of an occluded infarct artery 1 to 28 days after MI in stable patients had no incremental benefit beyond optimal medical therapy with aspirin, beta blockers, ACE inhibitors, and statins in preserving LV function and preventing subsequent cardiovascular events (Table 7).

8. Ancillary Therapy

2004 STEMI Guidelines—Section 6.3.1.6.8.1. Anticoagulants as Ancillary Therapy to Reperfusion Therapy

Since publication of the 2004 STEMI Guidelines,¹⁵ a number of studies have provided data that inform the recommendations on ancillary therapy to support reperfusion therapy for STEMI. In recognition that many agents capable of inhibiting the coagulation cascade may inhibit proteins other than thrombin, the writing group decided to change the nomenclature for this section. Therefore, the term anticoagulants is used in place of the prior term antithrombins. Also, although the material discussed below crosses several subsections in the 2004 STEMI Guidelines (Sections 6.3.1.6.8.1.1 and 6.3.1.6.8.1.2), because of a number of common issues, the writing group has elected to describe the updates on anticoagulant therapy collectively in this section.

Unfractionated heparin (UFH) is commonly administered to patients receiving fibrinolytic therapy. With limited evidence supporting the benefits of prolonged infusions of UFH and because of the progressive increase in the risk of heparin-induced thrombocytopenia (both rapid- and delayed-onset presentations),^{66,67} the 2004 STEMI Guidelines recommended that infusions of UFH be given routinely for 48 hours but be given for a longer period only in patients with an ongoing indication for anticoagulation.^{15,68,69} Although no new trials specifically focusing on UFH in STEMI were reported, a number of studies have compared alternative anticoagulant regimens with UFH or placebo. Importantly, each study tested a strategy that involved administering the new regimen (reviparin, fondaparinux, or enoxaparin) for the duration of the index hospitalization; that is, longer than

current practice and longer than recommended in the 2004 STEMI Guidelines. In addition, some of the new anticoagulant regimens used dosing schemes that were based on patient weight, age, or both. With the exception of reviparin, the details of the dosing schemes are noted in the recommendations above; the text below refers simply to the name of the anticoagulant regimen. Major efficacy and safety observations from the main trial and important subgroups reported to date are shown in Table 9.

The CREATE (Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta) trial was a randomized, double-blind comparison of a strategy of low-molecular-weight heparin (LMWH) reviparin versus placebo in 15 570 patients with STEMI enrolled in China and India⁷⁰ Although reviparin is not available for clinical use in North America, the writing group felt that the data from the CREATE trial were informative to clinicians and supported the data from the trials discussed subsequently. The dosing regimen for reviparin was as follows: for patients weighing less than 50 kg, subcutaneous injections of 3436 IU Ph Eur anti-Xa units every 12 hours; for patients weighing 50 to 75 kg, subcutaneous injections of 5153 IU Ph Eur anti-Xa units every 12

hours; and for patients weighing more than 75 kg, subcutaneous injections of 6871 IU Ph Eur anti-Xa units every 12 hours. Reviparin was continued for the duration of the index hospitalization, up to 1 week. Fibrinolytic therapy (predominantly non-fibrin-specific agents) was administered to 73% of the CREATE trial population, and it was recommended that the study drugs be started within 15 minutes of initiation of fibrinolysis. A total of 76% of the trial population received blinded study therapy for 7 days (see Table 9).

The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial was an international, randomized, double-blind comparison of fondaparinux, a synthetic factor Xa inhibitor, versus control therapy (either placebo or UFH) in 12 092 patients enrolled in 41 countries.⁷ Patients for whom the treating physician thought UFH was not indicated (e.g., non-fibrin-specific fibrinolytic administered) were enrolled in stratum I and received placebo in the control arm; patients for whom the treating physician thought UFH was indicated (e.g., fibrin-specific fibrinolytic administered or primary PCI performed) were enrolled in stratum II and received UFH in the control arm. The median duration of fondaparinux therapy was 8 days in stratum I and 7 days in

Table 8. Updates to Section 6.3.1.6.8.1: Anticoagulants as Ancillary Therapy to Reperfusion Therapy

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|-------------------------------------|---|--------------------|
| | Class I | |
| | 1. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours (<i>Level of Evidence: C</i>) and preferably for the duration of the index hospitalization, up to 8 days (regimens other than UFH are recommended if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). (<i>Level of Evidence: A</i>) Anticoagulant regimens with established efficacy include: a. UFH (initial intravenous bolus 60 U per kg [maximum 4000 U]) followed by an intravenous infusion of 12 U per kg per hour (maximum 1000 U per hour) initially, adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.0 times control (approximately 50 to 70 seconds) (<i>Level of Evidence: C</i>). (Note: the available data do not suggest a benefit of prolonging the duration of the infusion of UFH beyond 48 hours in the absence of ongoing indications for anticoagulation; more prolonged infusions of UFH increase the risk of development of heparin-induced thrombocytopenia.) b. Enoxaparin (provided the serum creatinine is less than 2.5 mg per dL in men and 2.0 mg per dL in women): for patients less than 75 years of age, an initial 30 mg intravenous bolus is given, followed 15 minutes later by subcutaneous injections of 1.0 mg per kg every 12 hours; for patients at least 75 years of age, the initial intravenous bolus is eliminated and the subcutaneous dose is reduced to 0.75 mg per kg every 12 hours. Regardless of age, if the creatinine clearance (using the Cockcroft-Gault formula) during the course of treatment is estimated to be less than 30 mL per minute, the subcutaneous regimen is 1.0 mg per kg every 24 hours. Maintenance dosing with enoxaparin should be continued for the duration of the index hospitalization, up to 8 days. (<i>Level of Evidence: A</i>) c. Fondaparinux (provided the serum creatinine is less than 3.0 mg per dL): initial dose 2.5 mg intravenously; subsequently subcutaneous injections of 2.5 mg once daily. Maintenance dosing with fondaparinux should be continued for the duration of the index hospitalization, up to 8 days. (<i>Level of Evidence: B</i>) | New recommendation |
| | 2. For patients undergoing PCI after having received an anticoagulant regimen, the following dosing recommendations should be followed: a. For prior treatment with UFH, administer additional boluses of UFH as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (<i>Level of Evidence: C</i>) Bivalirudin may also be used in patients treated previously with UFH. (<i>Level of Evidence: C</i>) b. For prior treatment with enoxaparin, if the last subcutaneous dose was administered within the prior 8 hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered at least 8 to 12 hours earlier, an intravenous dose of 0.3 mg per kg of enoxaparin should be given. (<i>Level of Evidence: B</i>) c. For prior treatment with fondaparinux, administer additional intravenous treatment with an anticoagulant possessing anti-IIa activity taking into account whether GP IIb/IIIa receptor antagonists have been administered. (<i>Level of Evidence: C</i>) | New recommendation |
| | Class III | |
| | 1. Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered. (<i>Level of Evidence: C</i>) | New recommendation |

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

Table 9. Trials of Anticoagulants for STEMI

| Trial (Drug) | STEMI Cohorts Studied | Efficacy Observations | Safety Observations | Transition to PCI | | | | | | | | | | | | | | | | | | | | | | | | |
|--|--|--|---------------------------------|---|-------------|-------------|---------------------|-----------|--|--------------|--|---------------------|---------|---|--------------|---------------------|----------|---------------------|------|---|-----------|---------|---------------------|-----------|---------|--|---------------------|--|
| CREATE (reviparin) ⁷⁰ N = 15 570 | Fibrinolysis (N = 11 355) Primary PCI (N = 949) No reperfusion (N = 3325) | Death/MI/Stroke (Day 7) | Life-Threatening Bleeds (Day 7) | Protocol recommended open-label UFH ⁵⁴ | | | | | | | | | | | | | | | | | | | | | | | | |
| | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>N = 7780</td> <td>N = 7790</td> </tr> <tr> <td>7 d: 9.6%</td> <td>7 d: 11.0%</td> </tr> <tr> <td colspan="2">HR 0.87</td> </tr> <tr> <td colspan="2">95% CI 0.79 to 0.96</td> </tr> <tr> <td>30 d: 11.8%</td> <td>30 d: 13.6%</td> </tr> <tr> <td colspan="2">HR 0.87</td> </tr> <tr> <td colspan="2">95% CI 0.79 to 0.95</td> </tr> </table> | Reviparin | | Placebo | N = 7780 | N = 7790 | 7 d: 9.6% | 7 d: 11.0% | HR 0.87 | | 95% CI 0.79 to 0.96 | | 30 d: 11.8% | 30 d: 13.6% | HR 0.87 | | 95% CI 0.79 to 0.95 | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>7 d: 0.9%</td> <td>7 d: 0.4%</td> </tr> <tr> <td colspan="2">HR 2.49</td> </tr> <tr> <td colspan="2">95% CI 1.61 to 3.87</td> </tr> </table> | Reviparin | Placebo | 7 d: 0.9% | 7 d: 0.4% | HR 2.49 | | 95% CI 1.61 to 3.87 | |
| | | Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | |
| N = 7780 | N = 7790 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 d: 9.6% | 7 d: 11.0% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.87 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.79 to 0.96 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 d: 11.8% | 30 d: 13.6% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.87 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.79 to 0.95 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 d: 0.9% | 7 d: 0.4% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 2.49 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 1.61 to 3.87 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Reperfused Cohort</i> | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>30 d: 11.0%</td> <td>30 d: 12.3%</td> </tr> <tr> <td colspan="2">HR 0.90</td> </tr> <tr> <td colspan="2">95% CI 0.81 to 1.01</td> </tr> </table> | Reviparin | Placebo | 30 d: 11.0% | 30 d: 12.3% | HR 0.90 | | 95% CI 0.81 to 1.01 | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>30 d: 1.1%</td> <td>30 d: 0.4%</td> </tr> <tr> <td colspan="2">HR N/A</td> </tr> </table> | Reviparin | Placebo | 30 d: 1.1% | 30 d: 0.4% | HR N/A | | | | | | | | | | | | |
| Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 d: 11.0% | 30 d: 12.3% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.90 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.81 to 1.01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 d: 1.1% | 30 d: 0.4% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR N/A | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Nonreperfused Cohort</i> | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>30 d: 15.0%</td> <td>30 d: 18.3%</td> </tr> <tr> <td colspan="2">HR 0.79</td> </tr> <tr> <td colspan="2">95% CI 0.65 to 0.95</td> </tr> </table> | Reviparin | Placebo | 30 d: 15.0% | 30 d: 18.3% | HR 0.79 | | 95% CI 0.65 to 0.95 | | <table border="1"> <tr> <td>Reviparin</td> <td>Placebo</td> </tr> <tr> <td>30 d: 0.1%</td> <td>30 d: 0.1%</td> </tr> <tr> <td colspan="2">HR N/A</td> </tr> </table> | Reviparin | Placebo | 30 d: 0.1% | 30 d: 0.1% | HR N/A | | | | | | | | | | | | |
| Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 d: 15.0% | 30 d: 18.3% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.79 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.65 to 0.95 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Reviparin | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 30 d: 0.1% | 30 d: 0.1% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR N/A | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| OASIS-6 (fondaparinux) ^{7,83a,83b} N = 12 092 | Fibrinolysis (N = 5436) (Non-fibrin-specific 4561; fibrin-specific 875) Primary PCI (N = 3789) No reperfusion (N = 2867) | Death/MI (Day 30) | Severe Hemorrhage (Day 9) | UFH (guided by ACT) for control subjects in Stratum II and supplemental 2.5 to 5.0 mg IV bolus of fondaparinux (depending on whether subject received open-label UFH and/or GP IIb/IIIa inhibitors before randomization) in the fondaparinux group. Drugs were administered in double-blind fashion during PCI ⁶ . | | | | | | | | | | | | | | | | | | | | | | | | |
| | | <table border="1"> <tr> <td>Fondaparinux</td> <td>Control</td> </tr> <tr> <td>N = 6036</td> <td>N = 6056</td> </tr> <tr> <td>9.7%</td> <td>11.2%</td> </tr> <tr> <td colspan="2">HR 0.86</td> </tr> <tr> <td colspan="2">95% CI 0.77 to 0.96</td> </tr> </table> | Fondaparinux | | Control | N = 6036 | N = 6056 | 9.7% | 11.2% | HR 0.86 | | 95% CI 0.77 to 0.96 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>Control</td> </tr> <tr> <td>N = 6036</td> <td>N = 6056</td> </tr> <tr> <td>1.0%</td> <td>1.3%</td> </tr> <tr> <td colspan="2">HR 0.77</td> </tr> <tr> <td colspan="2">95% CI 0.55 to 1.08</td> </tr> </table> | Fondaparinux | Control | N = 6036 | N = 6056 | 1.0% | 1.3% | HR 0.77 | | 95% CI 0.55 to 1.08 | | | | | |
| | | Fondaparinux | Control | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | N = 6036 | N = 6056 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | 9.7% | 11.2% | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | HR 0.86 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | 95% CI 0.77 to 0.96 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | Control | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N = 6036 | N = 6056 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.0% | 1.3% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.77 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.55 to 1.08 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Stratum I</i> | | Severe Hemorrhage (Day 9) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <tr> <td>Fondaparinux</td> <td>Placebo</td> </tr> <tr> <td>11.2%</td> <td>14.0%</td> </tr> <tr> <td colspan="2">HR 0.79</td> </tr> <tr> <td colspan="2">95% CI 0.68 to 0.92</td> </tr> </table> | Fondaparinux | Placebo | 11.2% | 14.0% | HR 0.79 | | 95% CI 0.68 to 0.92 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>Placebo</td> </tr> <tr> <td>1.0%</td> <td>1.6%</td> </tr> <tr> <td colspan="2">HR 0.63</td> </tr> <tr> <td colspan="2">95% CI 0.40 to 1.02</td> </tr> </table> | Fondaparinux | Placebo | 1.0% | 1.6% | HR 0.63 | | 95% CI 0.40 to 1.02 | | | | | | | | | | | | |
| Fondaparinux | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 11.2% | 14.0% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.79 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.68 to 0.92 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.0% | 1.6% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.63 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.40 to 1.02 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Stratum II</i> | | Severe Hemorrhage (Day 9) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>8.3%</td> <td>8.7%</td> </tr> <tr> <td colspan="2">HR 0.96</td> </tr> <tr> <td colspan="2">95% CI 0.81 to 1.13</td> </tr> </table> | Fondaparinux | UFH | 8.3% | 8.7% | HR 0.96 | | 95% CI 0.81 to 1.13 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>1.1%</td> <td>1.1%</td> </tr> <tr> <td colspan="2">HR 0.95</td> </tr> <tr> <td colspan="2">95% CI 0.59 to 1.52</td> </tr> </table> | Fondaparinux | UFH | 1.1% | 1.1% | HR 0.95 | | 95% CI 0.59 to 1.52 | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8.3% | 8.7% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.96 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.81 to 1.13 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.1% | 1.1% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.95 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.59 to 1.52 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Non-Fibrin-Specific Lytics</i> | | Severe Hemorrhage (Day 30) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <tr> <td>Fondaparinux</td> <td>Placebo</td> </tr> <tr> <td>10.7%</td> <td>13.8%</td> </tr> <tr> <td colspan="2">HR 0.76</td> </tr> <tr> <td colspan="2">95% CI 0.64 to 0.90</td> </tr> </table> | Fondaparinux | Placebo | 10.7% | 13.8% | HR 0.76 | | 95% CI 0.64 to 0.90 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>Placebo</td> </tr> <tr> <td>1.2%</td> <td>2.0%</td> </tr> <tr> <td colspan="2">HR 0.60</td> </tr> <tr> <td colspan="2">95% CI 0.37 to 0.97</td> </tr> </table> | Fondaparinux | Placebo | 1.2% | 2.0% | HR 0.60 | | 95% CI 0.37 to 0.97 | | | | | | | | | | | | |
| Fondaparinux | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10.7% | 13.8% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.76 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.64 to 0.90 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.2% | 2.0% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.60 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.37 to 0.97 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Fibrin-Specific Lytics</i> | | Severe Hemorrhage (Day 30) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>12.1%</td> <td>12.1%</td> </tr> <tr> <td colspan="2">HR 1.01</td> </tr> <tr> <td colspan="2">95% CI 0.69 to 1.48</td> </tr> </table> | Fondaparinux | UFH | 12.1% | 12.1% | HR 1.01 | | 95% CI 0.69 to 1.48 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>1.7%</td> <td>2.5%</td> </tr> <tr> <td colspan="2">HR 0.67</td> </tr> <tr> <td colspan="2">95% CI 0.26 to 1.73</td> </tr> </table> | Fondaparinux | UFH | 1.7% | 2.5% | HR 0.67 | | 95% CI 0.26 to 1.73 | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12.1% | 12.1% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 1.01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.69 to 1.48 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.7% | 2.5% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 0.67 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.26 to 1.73 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>Primary PCI</i> | | Severe Hemorrhage (Day 9) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>6.1%</td> <td>5.1%</td> </tr> <tr> <td colspan="2">HR 1.20</td> </tr> <tr> <td colspan="2">95% CI 0.91 to 1.57</td> </tr> </table> | Fondaparinux | UFH | 6.1% | 5.1% | HR 1.20 | | 95% CI 0.91 to 1.57 | | <table border="1"> <tr> <td>Fondaparinux</td> <td>UFH</td> </tr> <tr> <td>2.2%</td> <td>1.7%</td> </tr> <tr> <td colspan="2">HR 1.30</td> </tr> <tr> <td colspan="2">95% CI 0.81 to 2.08</td> </tr> </table> | Fondaparinux | UFH | 2.2% | 1.7% | HR 1.30 | | 95% CI 0.81 to 2.08 | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6.1% | 5.1% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 1.20 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.91 to 1.57 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fondaparinux | UFH | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2.2% | 1.7% | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HR 1.30 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 95% CI 0.81 to 2.08 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table 9. Continued

| Trial (Drug) | STEMI Cohorts Studied | Efficacy Observations | | Safety Observations | | Transition to PCI | | |
|---|--|-------------------------------------|------------|----------------------------|------------|--|--|--|
| OASIS-6 (Continued) | | <i>No Reperfusion</i> | | | | | | |
| | | Stratum I | | Stratum I/Stratum II | | | | |
| | | | | Severe Hemorrhage (Day 30) | | | | |
| | | Fondaparinux | Placebo | Fondaparinux | Control | | | |
| | | N = 1458 | N = 1409 | N = 1458 | N = 1409 | | | |
| | | 12.9% | 14.4% | 1.5% | 2.1% | | | |
| | | HR 0.88 | | HR 0.76 | | | | |
| | | 95% CI 0.65 to 1.19 | | 95% CI 0.42 to 1.36 | | | | |
| | | Stratum II | | | | | | |
| | | Fondaparinux | UFH | | | | | |
| | | 11.7% | 15.5% | | | | | |
| | | HR 0.74 | | | | | | |
| | | 95% CI 0.57 to 0.97 | | | | | | |
| EXTRACT-TIMI 25 (enoxaparin) N = 20 506 ^{6,73,83c,83d} | Alteplase (N = 11 175) Tenecteplase (N = 3986) Retepulse (N = 1122) Streptokinase (N = 4139) None (N = 57) | Death/MI (Day 30) | | Severe Hemorrhage (Day 30) | | UFH (guided by ACT) in subjects allocated to UFH and supplemental IV bolus of 0.3 mg per kg enoxaparin in subjects allocated to enoxaparin if last subcutaneous dose was 8 to 12 hours earlier. Drugs administered in double-blind fashion during PCI ^{56,57} . | | |
| | | Enoxaparin | UFH | Enoxaparin | UFH | | | |
| | | N = 10 256 | N = 10 223 | N = 10 176 | N = 10 151 | | | |
| | | 9.9% | 12.0% | 2.1% | 1.4% | | | |
| | | RR 0.83 | | RR 1.53 | | | | |
| | | 95% CI 0.77 to 0.90 | | 95% CI 1.23 to 1.89 | | | | |
| | | Age Less Than 75 Years (all lytics) | | | | | | |
| | | | | Severe Hemorrhage (Day 30) | | | | |
| | | Enoxaparin | UFH | Enoxaparin | UFH | | | |
| | | 7.9% | 9.9% | 1.9% | 1.1% | | | |
| RR 0.80 | | RR 1.67 | | | | | | |
| 95% CI 0.72 to 0.87 | | 95% CI 1.31 to 2.13 | | | | | | |
| Age 75 Years or Older (all lytics) | | | | | | | | |
| | | Severe Hemorrhage (Day 30) | | | | | | |
| Enoxaparin | UFH | Enoxaparin | UFH | | | | | |
| 24.8% | 26.3% | 3.3% | 2.9% | | | | | |
| RR 0.94 | | RR 1.15 | | | | | | |
| 95% CI 0.82 to 1.08 | | 95% CI 0.74 to 1.78 | | | | | | |
| Fibrin-Specific Lytics (all ages) | | | | | | | | |
| | | Severe Hemorrhage (Day 30) | | | | | | |
| Enoxaparin | UFH | Enoxaparin | UFH | | | | | |
| 9.8% | 12.0% | 2.0% | 1.2% | | | | | |
| OR adj 0.78 | | RR 1.89 | | | | | | |
| 95% CI 0.70 to 0.87 | | 95% CI 1.43 to 2.51 | | | | | | |
| Non-Fibrin-Specific Lytics (all ages) | | | | | | | | |
| | | Severe Hemorrhage (Day 30) | | | | | | |
| Enoxaparin | UFH | Enoxaparin | UFH | | | | | |
| 10.2% | 11.8% | 2.4% | 2.0% | | | | | |
| OR adj 0.83 | | RR 1.38 | | | | | | |
| 95% CI 0.66 to 1.04 | | 95% CI 0.88 to 2.17 | | | | | | |
| PCI postlysis (rescue, urgent, elective) N = 4676 | | PCI Postlysis | | | | | | |
| | | | | Severe Hemorrhage (Day 30) | | | | |
| | | Enoxaparin | UFH | Enoxaparin | UFH | | | |
| | | 10.7% | 13.8% | 1.4% | 1.6% | | | |
| | | RR 0.77 | | RR 0.87 | | | | |
| | | 95% CI 0.66 to 0.90 | | 95% CI 0.55 to 1.39 | | | | |

ACT indicates activated clotting time; adj, adjusted; CI, confidence interval; CREATE, Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta; EXTRACT-TIMI 25, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction; GP, glycoprotein; HR, hazard ratio; kg, kilogram; MI, myocardial infarction; N, number; N/A, not available; OASIS, Organization to Assess Strategies for Ischemic Syndromes; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST-elevation myocardial infarction; and UFH, unfractionated heparin.

stratum II (compared with 45 hours of UFH). Within the trial population, 2867 patients (23.7%) did not receive any reperfusion therapy and, depending on physician preference, were enrolled in either stratum I or II (see Table 9).

The ExTRACT-TIMI 25 trial was an international, double-blind comparison of a strategy of enoxaparin versus UFH in 20 506 patients enrolled in 48 countries who presented within 6 hours after the onset of STEMI and for whom fibrinolytic therapy was planned.⁶ Because prior trials reported that bleeding with enoxaparin was increased in elderly patients, a novel dosing regimen was devised for patients 75 years of age or older, and strict attention was paid to dose reduction in patients with significantly impaired renal function to minimize the accumulation of anti-Xa activity.^{71,72} The median duration of treatment was 7 days with enoxaparin and 2 days for UFH (see Table 9).

Some patients who receive pharmacological reperfusion with a fibrinolytic are referred for PCI. Consideration must be given to the anticoagulant regimen to support PCI in the face of preceding (upstream) anticoagulant therapy. The CREATE, OASIS-6, and ExTRACT-TIMI 25 trials took different approaches to the selection of anticoagulants to support PCI. Both CREATE and OASIS-6 included subsets of patients undergoing primary PCI; ExTRACT-TIMI 25 did not study patients undergoing primary PCI. In CREATE, patients in both the reviparin and placebo groups received open-label UFH at the time of PCI. In OASIS-6, the protocol recommended an IV bolus of fondaparinux (2.5 to 5.0 mg, depending on whether the patient received open-label UFH and/or GP IIb/IIIa inhibitors before randomization) (see Table 9). The number of patients in whom catheter thrombosis was observed was 0 in the UFH group and 22 in the fondaparinux group (p less than 0.001).⁷ When the subset of patients who received both open-label UFH and fondaparinux was analyzed, the number of catheter thromboses was 0 in the UFH group and 2 in the fondaparinux group.

In ExTRACT-TIMI 25, patients were maintained on the allocated anticoagulant as they moved from the medical to PCI phase of treatment ($n=2178$) or received open-label anticoagulant at the treating physician's discretion if performed after 8 days ($n=2498$). Among the patients allocated to enoxaparin, a dose of 0.3 mg per kg was administered intravenously if the last subcutaneous dose was 8 to 12 hours earlier, whereas no additional enoxaparin was administered if the last subcutaneous dose was administered within the prior 8 hours. UFH was dosed according to the activated clotting time (ACT), using a target of 200 seconds for patients receiving a GP IIb/IIIa inhibitor and 250 seconds for those not receiving a GP IIb/IIIa inhibitor.⁷³ The main observations (Table 9) were the same whether the results were analyzed by intention to treat or by the actual anticoagulant received during the procedure (blinded study or open-label anticoagulant if PCI was performed after Day 8).⁷³

8.1. Conclusion

The writing group felt that several important messages emerged from the CREATE, OASIS-6, and ExTRACT-TIMI 25 trials, and these are reflected in the updated recommendations (Table 8) and summarized in Table 10. Anticoagulant

therapy is beneficial in patients with STEMI, and there is benefit in more prolonged anticoagulant therapy (duration of index hospitalization) in patients receiving fibrinolytics, as seen in the comparisons of reviparin versus placebo (CREATE), fondaparinux versus placebo (stratum I in OASIS-6), and enoxaparin versus UFH (ExTRACT-TIMI 25). The mechanism of benefit from a more prolonged anticoagulant regimen is probably multifactorial and includes a longer exposure to anticoagulants to prevent rethrombosis of the infarct artery and prevention of the rebound increase in events seen after abrupt discontinuation of UFH infusions. Concern was raised about a rebound increase in events after abrupt discontinuation of UFH infusions in patients with UA/NSTEMI,⁷⁴ but this also appears to occur in patients with STEMI.⁶ The optimum method of terminating treatment with UFH has not been rigorously established for patients with either UA/NSTEMI or STEMI, but it is common clinical practice to simply discontinue UFH infusions. Finally, when the new anticoagulant regimens are compared with UFH as an active control, the greater degree of inhibition of the proximal portion of the coagulation cascade may lead to a greater reduction in thrombin generation.

Of note, reviparin, enoxaparin, and fondaparinux all involve, at least in part, clearance via the renal route. Hence, the potential exists for accumulation of anti-Xa activity with increasing degrees of renal failure. On the basis of available data, recommendations have been formulated for baseline creatinine cut points when a patient is considered for one of the new regimens. Also, estimation of creatinine clearance should be calculated via the Cockcroft-Gault formula rather than the Modification of Diet and Renal Disease (MDRD) equation, because the former has been used to modify dosing in clinical trials.⁷⁵ The writing group endorses further research into the optimum anticoagulant regimen in patients with moderate degrees of renal dysfunction. This group has not been studied extensively and may be at an increased risk of bleeding, which has been seen in contemporary dosing regimens. The group also recommends head-to-head comparative studies to evaluate newer anticoagulant drugs (e.g., fondaparinux, enoxaparin, bivalirudin) to assess optimal anticoagulant therapy in patients with STEMI; such studies could provide more clinically useful information than comparisons against UFH or no anticoagulant.

When added to previous data, the benefits of anticoagulation therapy started concurrently with non-fibrin-specific fibrinolytic agents (e.g., streptokinase) seen with all 3 of the new anticoagulation regimens led the writing group to recommend the use of an anticoagulant across the spectrum of fibrinolytic agents in common clinical use.^{6,7,70,76,77}

When moving to PCI after fibrinolytic therapy, those patients who received upstream UFH or enoxaparin can continue to receive those anticoagulants in a seamless fashion (i.e., without crossover to another agent) using the dosing regimens listed in the recommendations.⁷³ On the basis of the reports of catheter thrombosis with fondaparinux alone during primary PCI in OASIS-6 and the experience with fondaparinux in the OASIS-5 trial,⁷⁸ the writing group thought fondaparinux should not be used as the sole anticoagulant during PCI but should be coupled with an additional

Table 10. Summary of Observations From Trials of Anticoagulants for STEMI

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

*See text for further discussion and subgroup analysis.

†Definitions of significant bleeds varied among trials. Consult original references for details.

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

agent that has anti-IIa activity to ameliorate the risk of catheter complications. Although bivalirudin and UFH are potential options for supplemental anticoagulation with fondaparinux, the available experience, albeit limited, is largely with UFH. The only available data from the CREATE trial that bear on this point are with UFH.

Given the complexities of the characteristics of the individual agents and their actions on the coagulation cascade, clinicians are cautioned about extrapolating any of the observations with agents discussed in this update to other anticoagulant regimens. In particular, as noted by the FDA, LMWHs are sufficiently distinct that they should be evaluated individually rather than considered as a class of interchangeable agents.⁷⁹

The writing group also advises clinicians against drawing comparisons between the new anticoagulant regimens across trials because of the nonrandomized nature of such comparisons and the inability to ensure comparability of baseline characteristics for the populations in the trials. Finally, the writing group strongly cautions clinicians against overinterpretation of subgroup analyses in the trials listed in Table 9 (e.g., reperfusion with either fibrinolytics or PCI versus no reperfusion; reperfusion with various categories of fibrinolytics; and comparison of the new anticoagulant strategy versus placebo or UFH). Subgroup comparisons are less statistically robust than the main trial results because of their nonrandomized nature, the lack of statistical power to discern true differences in treatment effects, and the need to account for multiple comparisons. Nonsignificant interaction tests should not be used to definitively assert a lack of heterogeneity of treatment effects across subgroups, as such analyses are relatively weak statistical tests, especially in the case of small sample sizes in subgroups.^{80–83} In the case of the data in Table 9, an additional layer of complexity—a mixture of comparisons between placebo and an active comparator (UFH)—was introduced. The approach taken in Table 9 was to provide the point estimate and 95% CI of the treatment

effect in various subgroups to allow readers to see the range of possible treatment effects.⁸²

The writing group encourages randomization of additional patients in future trials to clarify a number of questions, such as 1) the benefits of reviparin compared with UFH in patients receiving fibrin-specific fibrinolytics or undergoing PCI, 2) the relative benefits of fondaparinux compared with UFH in patients receiving non-fibrin-specific and fibrin-specific fibrinolytics, as well as those patients not undergoing reperfusion, and 3) the relative benefits of enoxaparin compared with UFH in patients undergoing primary PCI and those not receiving reperfusion therapy.

9. Thienopyridines

The 2004 STEMI Guidelines made no specific recommendation related to dual antiplatelet therapy with clopidogrel plus low-dose aspirin for a broad population of patients at high risk for atherothrombotic events. Clopidogrel has previously been shown to benefit patients with documented atherosclerosis (recent MI, recent stroke, established peripheral arterial disease, PCI, and NSTEMI). Since publication of the 2004 STEMI Guidelines, 2 trials have been reported that provide data supporting expansion of the use of clopidogrel to the STEMI end of the acute coronary syndrome spectrum.⁸⁴

The COMMIT-CCS-2 study randomized 45 852 patients within 24 hours of suspected MI at 1250 hospitals in China to 75 mg of clopidogrel daily (without a loading dose) or placebo in addition to 162 mg of aspirin daily.³ In the trial population, 93% had ST-segment elevation or bundle-branch block, 7% had ST-segment depression, and 54% were treated with fibrinolysis (predominantly urokinase). There was no upper age limit. The mean age was 61 years; 26% of patients were 70 years of age or older. Twenty-eight percent were women. The study drug treatment was to continue until hospital discharge or up to 4 weeks; mean treatment duration was 14.9 days (25th, 50th, and 75th percentiles: 9, 14, and 21

days, respectively). The composite primary end point of death, reinfarction, or stroke was reduced from 10.1% in the placebo group to 9.2% in the clopidogrel group (OR 0.91 [95% CI 0.86 to 0.97]; $p=0.002$). Benefit with clopidogrel tended to be seen in the subgroups of patients who did and did not receive fibrinolytic therapy. The co-primary end point of all-cause mortality was reduced from 8.1% in the placebo group to 7.5% in the clopidogrel group (OR 0.93 [95% CI 0.87 to 0.99]; $p=0.03$; NNT=167). The rate of cerebral and major noncerebral bleeding was 0.55% in the placebo group and 0.58% in the clopidogrel group ($p=0.59$).

The CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28) study randomized 3491 patients (18 to 75 years of age) receiving fibrinolytic therapy within 12 hours of STEMI to clopidogrel (300 mg oral loading dose; 75 mg oral daily maintenance dose) or placebo.⁹ The primary composite efficacy end point of an occluded infarct artery on angiography or death or recurrent MI before angiography (between 48 and 192 hours after the start of study medication) occurred in 21.7% of the placebo group and 15.0% of the clopidogrel group (OR 0.64 [95% CI 0.53 to 0.76]; p less than 0.001). The benefit of clopidogrel was driven largely by the reduction in rate of an occluded infarct artery, which appears to have been accomplished by preventing infarct-related reocclusion rather than by facilitating early reperfusion.⁸⁵ The rate of TIMI major bleeding through 30 days was 1.7% in the placebo group and 1.9% in the clopidogrel group ($p=0.80$). When interpreting the safety of clopidogrel, especially in the face of a loading dose of 300 mg, it is important to note that subjects were excluded from CLARITY-TIMI 28 if they had received more than 4000 U of UFH before randomization.

The patients in the clopidogrel arm of CLARITY-TIMI 28 who underwent PCI constitute a group who were pretreated with clopidogrel and provide a comparison with those in the

placebo arm who underwent PCI without pretreatment.⁸⁶ The composite end point of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after enrollment was 6.2% in the non-pretreatment group and 3.6% in the pretreatment group (OR 0.54 [95% CI 0.35 to 0.85]; $p=0.008$).⁸⁶ There was no significant difference in the rates of the composite of TIMI major or minor bleeding in the pretreatment versus non-pretreatment groups (2.0% vs. 1.9%; p greater than 0.99).

9.1. Conclusion

The writing group felt that the COMMIT-CCS-2 and CLARITY-TIMI 28 trials provided evidence for benefit of adding clopidogrel to aspirin in patients undergoing fibrinolytic therapy (Table 11). The COMMIT-CCS-2 trial also supported the use of clopidogrel in patients who were not receiving reperfusion therapy. Although the available data suggest that the oral maintenance dose should be 75 mg daily, uncertainty exists about the efficacy and safety of adding a loading dose to elderly patients (more than 75 years of age), especially when they receive a fibrinolytic. Thus, the writing group does not recommend a loading dose in the elderly who receive a fibrinolytic and endorses further research to define the optimum clopidogrel regimen in the elderly. On the basis of the CLARITY-TIMI 28 study, it appears that the administration of clopidogrel at the time of initial fibrinolytic therapy is of benefit when PCI is performed subsequently. No data are available from clinical trials regarding long-term clopidogrel treatment in STEMI patients. Extrapolating from experience in patients with UA/NSTEMI, as well as those patients undergoing coronary stenting, the writing committee felt that long-term therapy with clopidogrel (e.g., 1 year) can be useful in patients with STEMI (Class IIa; Level of Evidence: C) (Table 11). Clinicians should consult Figure 37 in Section 7.12.11 of the 2004 STEMI Guidelines for guid-

Table 11. Updates to Section 6.3.1.6.8.2.2: Thienopyridines

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|--|--|
| | Class I | |
| In patients taking clopidogrel for whom CABG is planned, the drug should be withheld for at least 5 days and preferably for 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. (Level of Evidence: B) | 1. Clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. (Level of Evidence: A) Treatment with clopidogrel should continue for at least 14 days. (Level of Evidence: B) | New recommendation |
| | 2. In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days and preferably for 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. (Level of Evidence: B) | 2004 recommendation remains current in 2007 Update |
| | Class IIa | |
| | 1. In patients less than 75 years of age who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel 300 mg. (Level of Evidence: C) (No data are available to guide decision making regarding an oral loading dose in patients 75 years of age or older.) | New recommendation |
| | 2. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. (Level of Evidence: C) | New recommendation |

CABG indicates coronary artery bypass graft, and STEMI, ST-elevation myocardial infarction.

Table 12. Updates to Section 7.4.5: Anticoagulants

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|---|--|--|
| | Class IIa | |
| It is reasonable that STEMI patients who are not undergoing reperfusion therapy and who do not have a contraindication to anticoagulation be treated with IV or subcutaneous UFH or with subcutaneous LMWH for at least 48 hours. In patients whose clinical condition necessitates prolonged bedrest and/or minimized activity, it is reasonable that treatment be continued until the patient is ambulatory. (Level of Evidence: C) | 1. It is reasonable for patients with STEMI who do not undergo reperfusion therapy to be treated with anticoagulant therapy (non-UFH regimen) for the duration of the index hospitalization, up to 8 days. (Level of Evidence: B) Convenient strategies that can be used include those with LMWH (Level of Evidence: C) or fondaparinux (Level of Evidence: B) using the same dosing regimens as for patients who receive fibrinolytic therapy. See Section 6.3.1.6.8.1. | Modified recommendation (changed LOE and text) |

IV indicates intravenous; LMWH, low-molecular-weight heparin; LOE, level of evidence; STEMI, ST-elevation myocardial infarction; and UFH, unfractionated heparin.

ance when the patient has concurrent indications for oral anticoagulation.¹⁵

In August 2006, the FDA approved the use of clopidogrel for the treatment of patients with STEMI to reduce the rate of death from any cause and the rate of the combined end point of death, reinfarction, or stroke.⁸⁷

10. Anticoagulants

In the 2004 STEMI Guidelines, anticoagulant therapy with UFH was recommended for patients not receiving reperfusion with the goal of reducing mortality and reinfarction rates. In patients with UA/NSTEMI, treatment with LMWH is recommended with a similar goal, as well as for prevention of episodes of recurrent ischemia. Since publication of the 2004 STEMI Guidelines, 2 trials (CREATE and OASIS-6) have extended the database on which such recommendations were formulated by providing evidence of the benefit of anticoagulant therapy in STEMI patients who do not receive reperfusion therapy (see Tables 9 and 10).

Although 2 contemporary trials provided internally consistent findings of benefit of prolonged anticoagulant therapy (duration of the index hospitalization) in patients not receiving reperfusion therapy, the nonreperfusion groups were subgroups that represented only about 22% of the trial populations. Also, the patients were enrolled largely at sites that may have had different practice patterns than in North America, and there is uncertainty about the exact magnitude of the treatment effect of anticoagulants in the absence of more widespread use of clopidogrel. Because of these issues, the writing group concluded that a Class IIa, Level of Evidence: B recommendation should be assigned (Table 12). Convenient strategies that may be used include those with LMWH (Level of Evidence: C) or fondaparinux (Level of

Evidence: B) using the same dosing regimens as those for patients who receive fibrinolytic therapy (Table 12). See the 2004 STEMI Guidelines, Section 8 (updates to Section 6.3.1.6.8.1).¹⁵

11. Invasive Evaluation

The committee has revised the recommendations for invasive evaluation (Table 13).

12. Secondary Prevention

Table 14 contains revised recommendations adapted from the 2006 AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease.¹¹ This table replaces Table 32 from the 2004 STEMI Guidelines.¹⁵ Classes of recommendation and a corresponding level of evidence have been added for all recommendations. New recommendations for clopidogrel have been added to the section on antiplatelet agents/anticoagulants: clopidogrel 75 mg per day should be added to aspirin in patients with STEMI for at least 14 days whether patients undergo reperfusion with fibrinolysis or do not receive reperfusion therapy (i.e., all post-PCI nonstented STEMI patients). The benefits of clopidogrel are likely to continue with longer duration of treatment, although there are no data from randomized controlled trials beyond 30 days. This section has also been modified slightly to reflect the recent evidence on aspirin dosage for patients who have undergone PCI with stent placement.

Other changes since the 2001 AHA/ACC Secondary Prevention Guidelines⁸⁸ include the addition of recommended daily physical activity, a recommendation for lowered low-density lipoprotein cholesterol, and a new recommendation for an annual influenza vaccination.

Table 13. Updates to Section 7.11.6: Invasive Evaluation

| 2004 STEMI Guideline Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|--|--|
| | Class IIb | |
| Catheterization and revascularization may be considered as part of a strategy of routine coronary arteriography for risk assessment after fibrinolytic therapy. (Level of Evidence: B) | 1. Coronary arteriography may be considered as part of an invasive strategy for risk assessment after fibrinolytic therapy (Level of Evidence: B) or for patients not undergoing primary reperfusion. (Level of Evidence: C) | Modified recommendation (changed LOE and text) |

LOE indicates level of evidence, and STEMI, ST-elevation myocardial infarction.

Table 14. Secondary Prevention for Patients With Coronary and Other Vascular Disease

| 2004 STEMI Guideline Recommendations | 2007 STEMI Focused Update Recommendations | 2007 COR and LOE | Comments |
|---|---|------------------|--|
| Smoking | | | |
| 2007 Goal: Complete cessation, no exposure to environmental tobacco smoke | | | |
| Assess tobacco use. | 1. Status of tobacco use should be asked about at every visit. | <i>I (B)</i> | Modified recommendation (changed text) |
| Strongly encourage patient and family to stop smoking and to avoid secondhand smoke. | 2. Every tobacco user and family members who smoke should be advised to quit at every visit. | <i>I (B)</i> | Modified recommendation (changed text) |
| Provide counseling, pharmacological therapy (including nicotine replacement and bupropion), and formal smoking cessation programs as appropriate. (See Section 7.12.4 in the 2004 STEMI Guideline for further discussion.) | 3. The tobacco user's willingness to quit should be assessed. | <i>I (B)</i> | New recommendation |
| | 4. The tobacco user should be assisted by counseling and developing a plan for quitting. | <i>I (B)</i> | Modified recommendation (changed text) |
| | 5. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and pharmacological treatment) should be arranged. | <i>I (B)</i> | Modified recommendation (changed text) |
| | 6. Exposure to environmental tobacco smoke at work and home should be avoided. | <i>I (B)</i> | New recommendation |
| Blood Pressure Control: | | | |
| 2007 Goal: Less than 140/90 mm Hg or less than 130/80 if patient has diabetes or chronic kidney disease | | | |
| If blood pressure is 120/80 mm Hg or greater, initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients. | 1. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is recommended to initiate or maintain lifestyle modification—weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. | <i>I (B)</i> | Modified recommendation (changed text) |
| If blood pressure is 140/90 mm Hg or greater, or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes, add blood pressure-reducing medications,* emphasizing the use of beta blockers and inhibitors of the renin-angiotensin-aldosterone system. (See Sections 7.12.6, 7.12.7, and 7.12.8 in 2004 STEMI Guideline.) ¹⁵ | 2. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure. | <i>I (A)</i> | Modified recommendation (changed text) |
| Lipid Management | | | |
| 2007 Goal: LDL-C substantially less than 100 mg per dL (if triglycerides are greater than or equal to 200 mg per dL, non-HDL-C should be less than 130 mg per dL†.) | | | |
| Start dietary therapy in all patients (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol). | 1. Starting dietary therapy is recommended for all patients. Reduce intake of saturated fats (to less than 7% of total calories), trans fatty acids, and cholesterol (to less than 200 mg per day). | <i>I (B)</i> | Modified recommendation (changed text) |
| | 2. Adding plant stanol/sterols (2 g per day) and/or viscous fiber (greater than 10 g per day) is reasonable to further lower LDL-C. | <i>IIa (A)</i> | New recommendation |
| Promote physical activity and weight management. | 3. Promotion of daily physical activity and weight management is recommended. | <i>I (B)</i> | Modified recommendation (changed text) |
| Encourage increased consumption of omega-3 fatty acids. | 4. It may be reasonable to encourage increased consumption of omega-3 fatty acids in the form of fish† or in capsules (1 g per day) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction. | <i>IIb (B)</i> | Modified recommendation (changed text) |
| Assess fasting lipid profile in all patients, preferably within 24 h of STEMI. Add drug therapy according to the following guide. (See Section 7.12.2 in the STEMI 2004 Guideline.) | 5. A fasting lipid profile should be assessed in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiation of lipid-lowering medication is indicated as recommended below before discharge according to the following schedule: | <i>I (A)</i> | Modified recommendation (changed text) |
| LDL-C less than 100 mg/dL (baseline or on treatment), statins should be used to lower LDL-C. | • LDL-C should be less than 100 mg per dL. | <i>I (A)</i> | Modified recommendation (changed text) |
| | • Further reduction of LDL-C to less than 70 mg per dL is reasonable. | <i>IIa (A)</i> | New recommendation |

Table 14. Continued

| 2004 STEMI Recommendations | 2007 STEMI Recommendations | 2007 COR and LOE | Comments |
|---|---|------------------|--|
| LDL-C greater than or equal to 100 mg/dL (baseline or on treatment), intensify LDL-C-lowering therapy with drug treatment, giving preference to statins. | <ul style="list-style-type: none"> If baseline LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy§ should be initiated. | <i>I (A)</i> | Modified recommendation (changed text) |
| | <ul style="list-style-type: none"> If on-treatment LDL-C is greater than or equal to 100 mg per dL, intensifying LDL-lowering drug therapy (may require LDL-lowering drug combination) is recommended. | <i>I (A)</i> | Modified recommendation (changed text) |
| | <ul style="list-style-type: none"> If baseline LDL-C is 70 to 100 mg per dL, it is reasonable to treat to LDL-C less than 70 mg per dL. | <i>IIa (B)</i> | New recommendation |
| If triglycerides are greater than or equal to 150 mg/dL or HDL-C is less than 40 mg/dL, emphasize weight management and physical activity. Advise smoking cessation. | <ul style="list-style-type: none"> If triglycerides are greater than or equal to 150 mg per dL or HDL-C is less than 40 mg per dL, weight management, physical activity, and smoking cessation should be emphasized. | <i>I (B)</i> | Modified recommendation (changed text) |
| If triglycerides are 200 to 499 mg/dL after LDL-C-lowering therapy¶, consider adding fibrate or niacin.** | <ul style="list-style-type: none"> If triglycerides are 200 to 499 mg per dL,†† non-HDL-C target should be less than 130 mg per dL. | <i>I (B)</i> | Modified recommendation (changed text) |
| | <ul style="list-style-type: none"> If triglycerides are 200 to 499 mg per dL,†† further reduction of non-HDL-C to less than 100 mg per dL is reasonable. | <i>IIa (B)</i> | New recommendation |
| | 6. Therapeutic options to reduce non-HDL-C include: <ul style="list-style-type: none"> More intense LDL-C-lowering therapy is indicated. | <i>I (B)</i> | New recommendation |
| | <ul style="list-style-type: none"> Niacin** (after LDL-C-lowering therapy) can be beneficial. | <i>IIa (B)</i> | Modified recommendation (changed text) |
| | <ul style="list-style-type: none"> Fibrate therapy‡‡ (after LDL-C-lowering therapy) can be beneficial. | <i>IIa (B)</i> | Modified recommendation (changed text) |
| If triglycerides are greater than or equal to 500 mg/dL:***‡‡ Consider fibrate or niacin‡‡ before LDL-C-lowering therapy. **‡‡ Consider omega-3 fatty acids as adjunct for high triglycerides. (See Section 7.12.2 in the 2004 STEMI Guideline.) | 7. If triglycerides are greater than or equal to 500 mg per dL,††§§ therapeutic options indicated and useful to prevent pancreatitis are fibrate‡‡ or niacin** before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieving non-HDL-C less than 130 mg per dL is recommended. | <i>I (C)</i> | Modified recommendation (changed text) |
| Physical Activity | | | |
| Goal: 30 minutes, 7 days per week (minimum 5 days per week) | | | |
| Cardiac rehabilitation programs are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. (See Sections 7.12.12 and 8.2 in the 2004 STEMI Guideline.) | 1. Advising medically supervised programs (cardiac rehabilitation) for high-risk patients (e.g., recent acute coronary syndrome or revascularization, HF) is recommended. | <i>I (B)</i> | Modified recommendation (changed text) |
| Assess risk, preferably with exercise test, to guide prescription. | 2. For all patients, it is recommended that risk be assessed with a physical activity history and/or an exercise test to guide prescription. | <i>I (B)</i> | Modified recommendation (changed text) |
| Encourage minimum of 30 to 60 min of activity, preferably daily but at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work). | 3. For all patients, encouraging 30 to 60 minutes of moderate-intensity aerobic activity is recommended, such as brisk walking on most—preferably all—days of the week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work). | <i>I (B)</i> | Modified recommendation (changed text) |
| | 4. Encouraging resistance training 2 days per week may be reasonable. | <i>IIb (C)</i> | New recommendation |
| Weight Management | | | |
| Goal: BMI: 18.5 to 24.9 kg/m ² | | | |
| Waist circumference: Men less than 40 inches (102 cm), women less than 35 inches (89 cm) | | | |
| Calculate BMI and measure waist circumference as part of evaluation. Monitor response of BMI and waist circumference to therapy. | 1. It is useful to assess BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m ² . | <i>I (B)</i> | Modified recommendation (changed text) |

Table 14. Continued

| 2004 STEMI Recommendations | 2007 STEMI Recommendations | 2007 COR and LOE | Comments |
|---|---|------------------|--|
| Start weight management and physical activity as appropriate. Desirable BMI range is 18.5 to 24.9 kg/m ² . | 2. The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. | <i>I (B)</i> | Modified recommendation (changed text) |
| If waist circumference is greater than or equal to 35 inches in women or greater than or equal to 40 inches in men, initiate lifestyle changes and treatment strategies for metabolic syndrome. (See Section 7.12.3 of STEMI 2004 Guideline.) | 3. If waist circumference (measured horizontally at the iliac crest) is 35 inches (89 cm) or greater in women and 40 inches (102 cm) or greater in men, it is useful to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. | <i>I (B)</i> | Modified recommendation (changed text) |
| Diabetes Management Goal: HbA _{1c} less than 7% | | | |
| Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA _{1c} . | 1. It is recommended to initiate lifestyle and pharmacotherapy to achieve near-normal HbA _{1c} . | <i>I (B)</i> | Modified recommendation (changed text) |
| Treatment of other risk factors (e.g., physical activity, weight management, blood pressure, and cholesterol management). (See Section 7.12.9 in the 2004 STEMI Guideline.) | 2. Beginning vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management as recommended above) is beneficial. | <i>I (B)</i> | Modified recommendation (changed text) |
| | 3. Coordination of diabetic care with the patient's primary care physician or endocrinologist is beneficial. | <i>I (C)</i> | New recommendation |
| Antiplatelet Agents/Anticoagulants: Aspirin | | | |
| Start and continue indefinitely aspirin 75 to 162 mg/d if not contraindicated. | 1. For all post-PCI STEMI stented patients without aspirin resistance, allergy, or increased risk of bleeding, aspirin 162 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 75 mg to 162 mg daily. | <i>I (B)</i> | Modified recommendation (changed text) |
| | 2. In patients for whom the physician is concerned about risk of bleeding lower-dose 75 mg to 162 mg of aspirin is reasonable during the initial period after stent implantation. | <i>IIa (C)</i> | New recommendation |
| Antiplatelet Agents/Anticoagulants: Clopidogrel | | | |
| Consider clopidogrel 75 mg/d or warfarin if aspirin is contraindicated. | 1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). | <i>I (B)</i> | Modified recommendation (changed text) |
| | 2. For all STEMI patients not undergoing stenting (medical therapy alone or PTCA without stenting), treatment with clopidogrel should continue for at least 14 days. | <i>I (B)</i> | New recommendation |
| | 3. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. | <i>IIa (C)</i> | New recommendation |
| Antiplatelet Agents/Anticoagulants: Warfarin | | | |
| Manage warfarin to INR 2.5 to 3.5 in post-STEMI patients when clinically indicated or for those not able to take aspirin or clopidogrel. (See Sections 7.12.5 and 7.12.11 and Figure 37 in the 2004 STEMI Guideline for further details of antiplatelet and anticoagulant therapy at hospital discharge.) | 1. Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus). | <i>I (A)</i> | Modified recommendation (changed text) |
| | 2. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. | <i>I (B)</i> | New recommendation |

Table 14. Continued

| 2004 STEMI Recommendations | 2007 STEMI Recommendations | 2007 COR and LOE | Comments |
|--|---|------------------|--|
| | 3. In patients requiring warfarin, clopidogrel, and aspirin therapy, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75 mg dose of clopidogrel. | I (C) | New recommendation |
| | Renin-Angiotensin-Aldosterone System Blockers: ACE Inhibitors | | |
| ACE inhibitors in all patients indefinitely; start early in stable high-risk patients (anterior MI, previous MI, Killip class greater than or equal to II [S3 gallop, rales, radiographic CHF], LVEF less than 0.40). | 1. ACE inhibitors should be started and continued indefinitely in all patients recovering from STEMI with LVEF less than or equal to 40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. | I (A) | Modified recommendation (changed text) |
| | 2. ACE inhibitors should be started and continued indefinitely in patients recovering from STEMI who are not lower risk (lower risk defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated. | I (B) | New recommendation |
| | 3. Among lower risk patients recovering from STEMI (i.e., those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) use of ACE inhibitors is reasonable. | IIa (B) | New recommendation |
| | Renin-Angiotensin-Aldosterone System Blockers: Angiotensin Receptor Blockers | | |
| Angiotensin receptor blockers in patients who are intolerant of ACE inhibitors and with either clinical or radiological signs of heart failure or LVEF less than 0.40. | 1. Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF less than or equal to 40%. | I (A) | Modified recommendation (changed text) |
| | 2. It is beneficial to use angiotensin receptor blocker therapy in other patients who are ACE-inhibitor intolerant and have hypertension. | I (B) | New recommendation |
| | 3. Considering use in combination with ACE inhibitors in systolic dysfunction HF may be reasonable. | IIb (B) | New recommendation |
| | Renin-Angiotensin-Aldosterone System Blockers: Aldosterone Blockade | | |
| Aldosterone blockade in patients without significant renal dysfunction or hyperkalemia ^{¶¶} who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either diabetes or heart failure. (See Section 7.12.6 in the 2004 STEMI Guideline.) | 1. Use of aldosterone blockade in post-MI patients without significant renal dysfunction or hyperkalemia ^{¶¶} is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have an LVEF of less than or equal to 40%, and have either diabetes or HF. | I (A) | Modified recommendation (changed text) |
| | Beta Blockers | | |
| Start in all patients. Continue indefinitely. Observe usual contraindications. (See Section 7.12.7 in the 2004 STEMI Guideline.) | 1. It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated. | I (A) | Modified recommendation (changed text) |
| | Influenza Vaccination | | |
| | 1. Patients with cardiovascular disease should have an annual influenza vaccination. | I (B) | New recommendation |

Recommendations in bold type are those the writing committee felt deserved extra emphasis. The 2007 STEMI recommendations are written in complete sentences, in accordance with ACC/AHA Guidelines methodology. “No content change” indicates the updated recommendation now includes an LOE and COR and a verb consistent with that LOE and COR as outlined in the ACC/AHA LOE/COR table (Table 1).

*For compelling indications for individual drug classes in specific vascular diseases, see the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)^{87a}.

†Non-HDL-C indicates total cholesterol minus HDL-C.

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

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C less than 70 mg per dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C less than 70 mg per dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of greater than 50% in LDL-C levels by either statins or LDL-C-lowering drug combinations.

||Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin.

¶Treat to a goal of non-HDL-C substantially less than 130 mg per dL.

**Dietary supplement niacin must not be used as a substitute for prescription niacin.

††The use of resin is relatively contraindicated when triglycerides are greater than 200 mg per dL.

‡‡The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination.

§§Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are greater than 200 mg per dL.

|||Creatinine should be less than 2.5 mg per dL in men and less than 2.0 mg per dL in women.

¶¶Potassium should be less than 5.0 mEq/L.

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; COR, classification of recommendation; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Table 15. Updates to Section 7.12.5: Antiplatelet Therapy

| 2004 STEMI Guidelines Recommendation | 2007 STEMI Focused Update Recommendation | Comments |
|--|---|--|
| | Class I | |
| | 1. At the time of preparation for hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed and a stepped-care approach to pain management should be used for selection of treatments (Figure 4). Pain relief should begin with acetaminophen or aspirin, small doses of narcotics, or non-acetylated salicylates. (Level of Evidence: C) | New recommendation |
| | Class IIa | |
| | 1. It is reasonable to use non-selective NSAIDs such as naproxen if initial therapy with acetaminophen, small doses of narcotics, or non-acetylated salicylates is insufficient. (Level of Evidence: C) | New recommendation |
| | Class IIb | |
| | 1. NSAIDs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations where intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs. In all cases, the lowest effective doses should be used for the shortest possible time. (Level of Evidence: C) | New recommendation |
| | Class III | |
| Ibuprofen should not be used because it blocks the antiplatelet effects of aspirin. (Level of Evidence: C) | 1. NSAIDs with increasing degrees of relative COX-2 selectivity should not be administered to STEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief. (Level of Evidence: C) | Modified recommendation (changed text) |

COX-2 indicates cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs; and STEMI, ST-elevation myocardial infarction.

13. Antiplatelet Therapy

The selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk. The risk appears to be amplified in patients with established cardiovascular disease.^{15,18,19}

Gislason et al. analyzed the risk of rehospitalization for MI and death related to the use of NSAIDs, including selective COX-2 inhibitors, in patients with prior MI.¹⁷ All patients with first-time MI between 1995 and 2002 and all prescription claims for NSAIDs after discharge were identified from nationwide Danish administrative registers. The risk of death and rehospitalization for MI associated with the use of selective COX-2 inhibitors and nonselective NSAIDs was studied with the use of

multivariable proportional hazards models and case-crossover analysis. A total of 58 432 patients were discharged alive and included in the study; 9773 were rehospitalized for MI, and 16 573 died. A total of 5.2% of patients received rofecoxib; 4.3%, celecoxib; 17.5%, ibuprofen; 10.6%, diclofenac; and 12.7%, other NSAIDs. For any use of rofecoxib, celecoxib, ibuprofen, diclofenac, and other NSAIDs, the HR and 95% CI for death were 2.80 (2.41 to 3.25), 2.57 (2.15 to 3.08), 1.50 (1.36 to 1.67), 2.40 (2.09 to 2.80), and 1.29 (1.16 to 1.43), respectively. There were dose-related increases in risk of death for all the drugs and non-dose-dependent trends for increased risk of rehospitalization for MI associated with the use of both the selective COX-2 inhibitors and nonselective NSAIDs.¹⁷

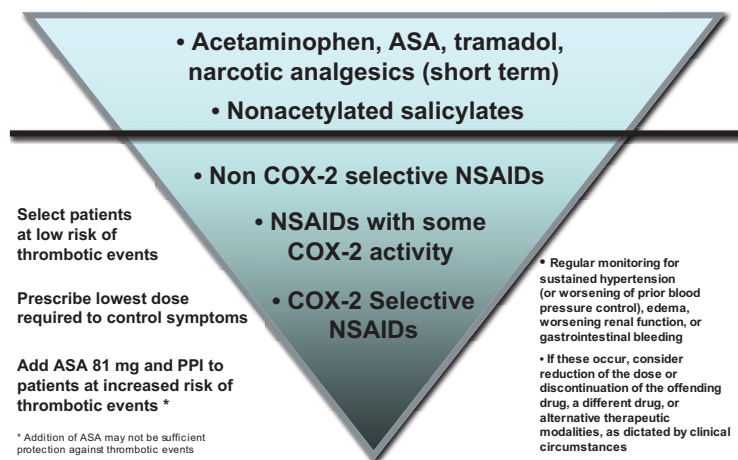


Figure 4. Stepped-Care Approach to Management of Musculoskeletal Symptoms. In patients with known cardiovascular disease or who are at risk for ischemic heart disease, clinicians should use a stepped-care approach to pharmacological therapy, focusing on agents with the lowest reported risk of cardiovascular events and then progressing toward other agents with consideration of the risk-benefit balance at each step. Once the decision is made to prescribe an NSAID (below the horizontal line), additional considerations assume importance as illustrated by the recommendations at the bottom left and right of the diagram. ASA indicates aspirin; COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs; and PPI, proton pump inhibitors. Reproduced with permission from Antman et al.²⁰

An AHA scientific statement on the use of NSAIDs concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk in the patient.²⁰ Nonpharmacological approaches were recommended as the first line of treatment, followed by the stepped-care approach to pharmacological therapy shown in Figure 4 (Table 15). Although not preferred, analgesic doses of aspirin may be a reasonable option for some patients. This approach provides an antiplatelet effect but confers a higher risk of bleeding than low-dose aspirin plus another analgesic.⁸⁹

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Appendix 1. Author Relationships With Industry—2007 Focused Update of the 2004 ACC/AHA Guidelines for the Treatment of Patients with ST-Elevation Myocardial Infarction

| Committee Member | Research Grant | Speakers' Bureau/ Honoraria | Stock Ownership | Board of Directors | Consultant/ Advisory Member |
|----------------------------|--|--|-----------------|--------------------|---|
| Dr. Elliott M. Antman* | Dr. Antman is a senior investigator in the TIMI Study Group, which received grants from the following sources: <ul style="list-style-type: none"> • Accumetrics • Amgen • AstraZeneca Pharmaceuticals • Bayer Healthcare • Beckman Coulter • Biosite • Bristol-Myers Squibb Pharmaceutical Research Institute • CV Therapeutics • Eli Lilly • GlaxoSmithKline • Inotek Pharmaceuticals Corporation • Integrated Therapeutics • Merck • Millennium Pharmaceuticals • National Institutes of Health • Novartis Pharmaceuticals • Nuvelo • Ortho-Clinical Diagnostics • Pfizer • Roche Diagnostics • Roche Diagnostics GmbH • Sanofi-Aventis† • Sanofi-Synthelabo Recherche • Schering-Plough Research Institute | <ul style="list-style-type: none"> • Eli Lilly • Sanofi-Aventis | None | None | <ul style="list-style-type: none"> • Sanofi-Aventis |
| Dr. Paul W. Armstrong‡ | <ul style="list-style-type: none"> • Boehringer Ingelheim† • Hoffmann-LaRoche Canada† • Portola† • Procter & Gamble/Alexion† • Sanofi-Aventis • Schering-Plough Research Institute† • Scios/Ortho Biotech† | <ul style="list-style-type: none"> • Hoffmann-LaRoche • KAI Pharmaceuticals • Sanofi-Aventis | None | None | <ul style="list-style-type: none"> • Abbott • ArgiNOx • Medicure† • TargeGen |
| Dr. Eric R. Bates | None | <ul style="list-style-type: none"> • Eli Lilly • Hoffman-LaRoche • PDL Biopharma • Sanofi-Aventis • Schering-Plough | None | None | <ul style="list-style-type: none"> • AstraZeneca • Datascope • Eli Lilly • GlaxoSmithKline • Sanofi-Aventis • The Medicines Co. |
| Dr. Lee A. Green | None | None | None | None | None |
| Dr. Lakshmi K. Halasyamani | None | None | None | None | None |
| Ms. Mary Hand | None | None | None | None | None |

| Committee Member | Research Grant | Speakers' Bureau/ Honoraria | Stock Ownership | Board of Directors | Consultant/ Advisory Member |
|--------------------------|---|--|-----------------|--------------------|---|
| Dr. Judith S. Hochman§ | <ul style="list-style-type: none"> • ArgiNOx Pharmaceutical • Eli Lilly | None | None | None | <ul style="list-style-type: none"> • Bristol-Myers Squibb • CV Therapeutics • Datascope • Eli Lilly • GlaxoSmithKline • Merck • Procter & Gamble • Sanofi-Aventis |
| Dr. Harlan M. Krumholz | <ul style="list-style-type: none"> • Agency for Healthcare Research and Quality • Colorado Foundation for Medical Care • Commonwealth Fund • NHLBI • Ripple Foundation • Robert Wood Johnson Foundation | None | None | None | <ul style="list-style-type: none"> • Alere • UnitedHealthcare |
| Dr. Gervasio A. Lamas§ | <ul style="list-style-type: none"> • Impulse Dynamics | <ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb • CV Therapeutics • GlaxoSmithKline • Medtronic • Novartis | None | None | <ul style="list-style-type: none"> • CV Therapeutics • Medtronic |
| Dr. Charles J. Mullany | None | None | None | None | None |
| Dr. David L. Pearle | None | <ul style="list-style-type: none"> • GlaxoSmithKline | None | None | None |
| Dr. Michael A. Sloan | None | <ul style="list-style-type: none"> • Boehringer Ingelheim | None | None | <ul style="list-style-type: none"> • Bayer HealthCare • Bristol-Myers Squibb • Terumo Cardiovascular |
| Dr. Sidney C. Smith, Jr. | None | <ul style="list-style-type: none"> • Sanofi-Aventis (Honorarium) | None | None | <ul style="list-style-type: none"> • Bristol-Myers Squibb • Eli Lilly • GlaxoSmithKline • Pfizer • Sanofi-Aventis |

This table represents the actual or potential relationships with industry that were reported. This table was updated in conjunction with all conference calls of the writing committee. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more 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 in this table are modest unless otherwise noted.

*Recused from voting on Section 8: Anticoagulants as Ancillary Therapy to Reperfusion Therapy and Section 10: Anticoagulants.

†Indicates a relationship valued at \$10 000 or more.

‡Recused from voting on Section 5: Facilitated PCI.

§Recused from voting on Section 7: PCI After Fibrinolysis or for Patients Not Undergoing Primary Reperfusion.

||Recused from voting on Section 13: Antiplatelet Therapy.

Appendix 2. Peer-Reviewer Relationships With Industry—2007 Focused Update of the 2004 ACC/AHA Guidelines for the Treatment of Patients with ST-Elevation Myocardial Infarction

| Peer Reviewer* | Representation | Research Grant | Speakers' Bureau | Stock Ownership | Board of Directors | Consultant/Advisory Member |
|-------------------------|---|---|--|-----------------|--------------------|--|
| Dr. Jeffrey L. Anderson | • Official Reviewer— ACC/AHA Task Force on Practice Guidelines | • AstraZeneca • Bristol-Myers Squibb/Sanofi- Aventis • Novartis • ThromboVision | Merck† | None | None | • Bristol-Myers Squibb/Sanofi- Aventis • Dia Dexus • Merck† • Novartis • ThromboVision Procter & Gamble |
| Dr. Vincent Carr | • Official Reviewer— ACCF Board of Governors | None | None | None | None | None |
| Dr. James deLemos | • Official Reviewer— AHA | None | • Bristol-Myers • Squibb/Sanofi- Aventis • Merck-Schering† • Pfizer† | None | None | • Bristol-Myers • Squibb/Sanofi- Aventis • Pfizer |
| Dr. David Holmes | • Official Reviewer— ACCF Board of Trustees | None | None | None | None | None |
| Dr. Sanjay Kaul | • Official Reviewer— AHA | None | None | None | None | None |
| Dr. Nick Fitterman | • Organizational Reviewer— American College of Physicians | None | None | None | None | None |
| Dr. Thomas F. Koinis | • Organizational Reviewer— American Association of Family Practice | None | None | None | None | • Merck |
| Dr. Robert C. Marshall | • Organizational Reviewer— American Association of Family Practice | None | None | None | None | None |
| Dr. Katherine Sherif | • Organizational Reviewer— American College of Physicians | • Novartis | None | None | None | • Novartis • Reliant |
| Dr. Mazen S. Abu-Fadel | • Content Reviewer— ACCF Cardiac Catheterization and Intervention Committee | None | • Novartis | None | None | None |
| Dr. Christopher Cannon | • Content Reviewer— ACC/AHA Acute Coronary Syndromes Data Standards Committee | • Accumetrics† • AstraZeneca† • Bristol-Myers Squibb† • GlaxoSmithKline† • Merck† • Sanofi-Aventis† • Schering-Plough† | • Accumetrics • AstraZeneca • Bristol-Myers Squibb • Merck • Pfizer • Sanofi-Aventis • Schering-Plough | None | None | • AstraZeneca • Bristol-Myers Squibb • GlaxoSmithKline • Merck • Pfizer • Sanofi-Aventis • Schering-Plough |
| Dr. John G. Canto | • Content Reviewer— Individual Review | • Pfizer • Schering-Plough† | • Bristol-Myers • Squibb† • CV Therapeutics • GlaxoSmithKline† • Pfizer† • Sanofi-Aventis† | None | None | • NRM/Genentech • Pfizer • Sanofi-Aventis |

| Peer Reviewer* | Representation | Research Grant | Speakers' Bureau | Stock Ownership | Board of Directors | Consultant/Advisory Member |
|--------------------------|--|--|--|-----------------|--------------------|--|
| Dr. Bernard R. Chaitman | • Content Reviewer—ACC/AHA Acute Coronary Syndromes Data Standards Committee | • CV Therapeutics • Pfizer | • AstraZeneca • CV Therapeutics† • Pfizer | None | None | • Bayer† • CV Therapeutics • Genentech • Lilly • Merck • Roche • Sanofi-Aventis |
| Dr. Kim Eagle | • Content Reviewer—AHA | • Blue Cross Blue Shield of Michigan • Biosite • Bristol-Myers Squibb • Hewlett Foundation • Mardigian Fund • Pfizer • Sanofi-Aventis • Varbedian Fund | None | None | None | • NHLBI/NIH • Pfizer • Sanofi-Aventis • Robert Wood Johnson Foundation |
| Dr. James J. Ferguson | • Content Reviewer—ACCF Cardiac Catheterization and Intervention Committee | • Eisai† • Sanofi-Aventis • The Medicines Co. | • Bristol-Myers Squibb • Sanofi-Aventis† • Schering-Plough | None | None | • Astellas • AstraZeneca • Bristol-Myers Squibb • Daiichi-Sankyo • Eisai • Eli Lilly • GlaxoSmithKline • Johnson & Johnson • Sanofi-Aventis • Schering-Plough • Takeda • Pharmaceuticals • The Medicines Co. • Therox |
| Dr. Michael A. Fifer | • Content Reviewer—AHA Acute Cardiac Care Committee | • Merck† | None | None | None | None |
| Dr. Robert A. Harrington | • Content Reviewer—Individual Review | • AstraZeneca • Bristol-Myers Squibb • Conor Med System • Cordis • GlaxoSmithKline • Lilly • Merck • Sanofi-Aventis • Schering-Plough • The Medicines Co. | None | None | None | • Schering-Plough |
| Dr. Sharon A. Hunt | • Content Reviewer—ACC/AHA Heart Failure Guidelines Committee | None | None | None | None | None |
| Dr. Hani Jneid | • Content Reviewer—AHA Diagnostic and Interventional Cardiac Catheterization Committee | • Pfizer† | None | None | None | None |
| Dr. Morton J. Kern | • Content Reviewer—ACC/AHA/SCAI PCI Guidelines Committee | None | • Radi Medical • Volcano Corp | None | None | • Bracco • Merit Medical |

| Peer Reviewer* | Representation | Research Grant | Speakers' Bureau | Stock Ownership | Board of Directors | Consultant/Advisory Member |
|-----------------------------|---|---|---|---------------------------------|--------------------|--|
| Dr. Frederick G. Kushner | • Content Reviewer—ACC/AHA STEMI Guidelines Committee and ACC/AHA Task Force on Practice Guidelines | None | None | • Johnson & Johnson • Pfizer | None | • AstraZeneca • Bristol-Myers Squibb • Merck • Novartis • Pfizer |
| Dr. Glenn N. Levine | • Content Reviewer—AHA Diagnostic and Interventional Catheterization Committee | None | None | None | None | • The Medicines Co. |
| Dr. George A. Mensah | • Content Reviewer—Individual Review | None | None | None | None | None |
| Dr. Brahmajee K. Nallamothu | • Content Reviewer—Individual Review | • Agency for Healthcare Research and Quality | None | None | None | None |
| Dr. Robert A. O'Rourke | • Content Reviewer—ACC/AHA Chronic Stable Angina Guidelines Committee | • Multiple drug companies funding BARI 2D and COURAGE trials | • Pfizer | None | None | • Aventis • Merck • Pfizer |
| Dr. Joseph P. Ornato | • Content Reviewer—ACC/AHA STEMI Guidelines Committee | None | • Bristol-Myers Squibb • Genentech • Sanofi-Aventis • ZOLL Circulation | None | None | • Genentech • ZOLL Circulation |
| Dr. Martha J. Radford | • Content Reviewer—ACC/AHA Acute Coronary Syndromes Data Standards Committee | None | None | None | None | None |
| Dr. Peter S. Rahko | • Content Reviewer—ACC/AHA Heart Failure Guidelines Committee | None | None | None | None | None |
| Dr. Rita F. Redberg | • Content Reviewer—ACC Prevention Committee | None | None | None | None | None |
| Dr. Barbara J. Riegel | • Content Reviewer—ACC/AHA Task Force on Practice Guidelines | None | None | None | None | None |
| Dr. Charanjit S. Rihal | • Content Reviewer—AHA Diagnostic and Interventional Cardiac Catheterization Committee | None | None | None | None | None |
| Dr. Matthew T. Roe | • Content Reviewer—Individual Review | • Bristol-Myers Squibb • Daiichi-Sankyo • Eli Lilly • KAI Pharmaceuticals • Portola • Pharmaceuticals • Sanofi-Aventis • Schering-Plough | • Bristol-Myers Squibb • Sanofi-Aventis • Schering-Plough | None | None | • Bristol-Myers Squibb • Daiichi-Sankyo • Eli Lilly • Genentech • KAI Pharmaceuticals • Novartis • Portola • Pharmaceuticals • Sanofi-Aventis • Schering-Plough |

| Peer Reviewer* | Representation | Research Grant | Speakers' Bureau | Stock Ownership | Board of Directors | Consultant/Advisory Member |
|----------------------------|--|---|---|--|--------------------|--|
| Dr. Allan M. Ross | • Content Reviewer— Individual Review | • Boehringer Ingelheim • Genentech • Roche | None | None | None | • Boehringer Ingelheim • Roche |
| Dr. Thomas Ryan | • Content Reviewer— Individual Review | None | • Bristol-Myers Squibb-Sanofi Pharmaceutic | None | None | • Arrow International |
| Dr. M. Eugene Sherman | • Content Reviewer— Board of Governors | None | • Abbott • GlaxoSmithKline • Novartis • Sanofi-Aventis • Takeda | • General Electric • Johnson & Johnson • Pfizer† | None | None |
| Dr. Samuel J. Shubrooks | • Content Reviewer— ACCF Board of Governors | None | None | None | None | None |
| Dr. Chittur A. Sivaram | • Content Reviewer— ACCF Board of Governors | None | None | None | None | None |
| Dr. W. Douglas Weaver | • Content Reviewer— STEMI/NSTEMI Performance Measures Committee | • Bristol-Myers Squibb • Johnson & Johnson • Procter & Gamble | None | None | None | • Data Safety Monitoring Committees for: • AstraZeneca • Boston Scientific • Genentech • Seredigm • The Medicines Co. |
| Dr. Janet F. Wyman | • Content Reviewer— ACCF Cardiac Catheterization and Intervention Committee | | | | | |
| Dr. Yerem Yeghiazarians | • Content Reviewer— AHA Diagnostic and Interventional Cardiac Catheterization Committee | None | • Pfizer • Sanofi-Aventis | None | None | None |

This table represents the relationships with industry that were disclosed at the time of peer review. 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% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more 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 in this table are modest unless otherwise noted.

*Names are listed in alphabetical order within each category of review.

†Significant (greater than \$10 000) relationship.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SCAI, Society for Coronary Angiography and Interventions; and STEMI, ST-elevation myocardial infarction.