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Acute ST-Segment Elevation Myocardial Infarction*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Shaun G. Goodman, MD; Venu Menon, MD; Christopher P. Cannon, MD, PhD; Gabriel Steg, MD, FCCP; E. Magnus Ohman, MD, FCCP; and Robert A. Harrington, MD, FCCP

This chapter about fibrinolytic, antiplatelet, and antithrombin treatment for acute ST-segment elevation (STE) myocardial infarction (MI) is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patient values may lead to different choices (for a full understanding of the grading see the chapter by Guyatt et al, CHEST 2008; 133[suppl]:123S–131S). Among the key recommendations in this chapter are the following: for patients with ischemic symptoms characteristic of acute MI of ≤ 12 h in duration and persistent STE, we recommend that all undergo rapid evaluation for reperfusion (primary percutaneous coronary intervention [PCI] or fibrinolytic) therapy and have a reperfusion strategy implemented promptly after contact with the health-care system (Grade 1A). For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h in duration and persistent STE, we recommend administration of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase over no fibrinolytic therapy (all Grade 1A). For patients with symptom duration ≤ 6 h, we recommend the administration of alteplase or tenecteplase over streptokinase (both Grade 1A). We recommend aspirin over no aspirin therapy followed by indefinite therapy (Grade 1A); we also recommend clopidogrel in addition to aspirin for up to 28 days (Grade 1A). In addition to aspirin and other antiplatelet therapies, we recommend the use of antithrombin therapy (eg, unfractionated heparin [UFH], enoxaparin, or fondaparinux) over no antithrombin therapy (Grade 1A), including for those patients receiving fibrinolysis (and regardless of which lytic agent is administered), primary PCI, or patients not receiving reperfusion therapy.

Key words: anticoagulant drugs; antiplatelet drugs; fibrinolytic therapy; myocardial infarction

Abbreviations: ACS = acute coronary syndrome; ACT = activated clotting time; APTT = activated partial thromboplastin time; BBB = bundle-branch block; CI = confidence interval; FTT = Fibrinolytic Therapy Trialists; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; HR = hazard ratio; ICH = intracranial hemorrhage; IRA = infarct-related artery; LMWH = low-molecular-weight heparin; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk; RRR = relative risk reduction; SC = subcutaneous; STE = ST-segment elevation; tPA = tissue plasminogen activator; UFH = unfractionated heparin
Summary of Recommendations

1.0 Reperfusion Therapy

1.0.1. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration and persistent STE, we recommend that all undergo rapid evaluation for reperfusion (primary PCI or fibrinolytic) therapy and have a reperfusion strategy implemented promptly after contact with the health-care system (Grade 1A).

1.1 Fibrinolysis

1.1.1. In patients with acute MI who are candidates for fibrinolytic therapy, we recommend administration as soon as possible (ideally within 30 min) after arrival to the hospital or first contact with the health-care system (Grade 1A).

1.1.2. In health-care settings where prehospital administration of fibrinolytic therapy is feasible, we recommend prehospital administration of fibrinolytic therapy (Grade 1A).

1.1.3. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration and persistent STE, we recommend administration of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase over no fibrinolytic therapy (all Grade 1A).

1.1.4. For patients with symptom duration ≤ 6 h, we recommend the administration of alteplase (Grade 1A) or tenecteplase (Grade 1A), and suggest reteplase (Grade 2B) over streptokinase.

1.1.5. For patients receiving fibrinolytic therapy, we suggest the use of a bolus agent (e.g., tenecteplase) to facilitate the ease of administration and potentially reduce the risk of non-intracranial hemorrhage (ICH)-related bleeding (reteplase) [Grade 2A].

1.1.6. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration, and left bundle-branch block (BBB) with associated STE changes, we recommend fibrinolytic therapy if primary PCI is not readily available (Grade 1B).

1.1.7. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration and ECG findings consistent with a true posterior MI, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.8. For high-risk patients with ongoing symptoms characteristic of acute MI or hemodynamic compromise and duration of 12 to 24 h who have persistent STE or left BBB with STE changes, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.9. In patients with any history of ICH, or with history of head trauma, or with ischemic stroke within the past 6 months, we recommend against administration of fibrinolytic therapy (Grade 1C).

2.1 Antiplatelet/Antithrombotic Therapy

Aspirin

2.1.1. For patients with acute STE MI whether or not they receive fibrinolytic therapy, we recommend aspirin (160 to 325 mg po) over no aspirin therapy at initial evaluation by health-care personnel (Grade 1A) followed by indefinite therapy (75 to 162 mg/d po) [Grade 1A].

2.2 Clopidogrel

2.2.1. For patients with acute STE MI, we recommend clopidogrel in addition to aspirin (Grade 1A). The recommended dosing for clopidogrel is 300 mg po for patients ≤ 75 years old and 75 mg po for patients > 75 years old if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/d po for up to 28 days (Grade 1A).

2.2.2. For patients with acute STE MI who have not received a coronary stent, we suggest that clopidogrel, 75 mg/d, could be continued beyond 28 days and up to 1 year (Grade 2B).

2.2.3. For patients undergoing primary PCI, we suggest clopidogrel in addition to aspirin with a recommended initial dosing of at least 300 mg (Grade 1B), followed by 75 mg/d daily (for duration of therapy, see chapter by Becker et al in this supplement).

2.3 Antithrombin Therapy

2.3.1. For patients with acute STE MI, in addition to aspirin and other antiplatelet therapies,
we recommend the use of antithrombin therapy over no antithrombin therapy (Grade 1A), including for those patients receiving fibrinolysis (and regardless of which lytic agent is administered), primary PCI, or patients not receiving reperfusion therapy.

2.4 UFH

2.4.1. For patients receiving streptokinase, we suggest administration of either IV UFH (5,000-U bolus followed by 1,000 U/h for patients > 80 kg, 800 U/h for < 80 kg) with a target activated partial thromboplastin time (APTT) of 50 to 75 s or subcutaneous (SC) UFH (12,500 U q12h) over no UFH therapy for 48 h (both Grade 1B).

2.4.2. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis in acute MI, we recommend administration of weight-adjusted heparin (60 U/kg bolus for a maximum of 4,000 U, followed by 12 U/kg/h [1,000 U/h maximum]) adjusted to maintain an APTT of 50 to 70 s for 48 h (Grade 1B).

2.4.3. For patients with STE MI undergoing primary PCI, we recommend administration of IV UFH over no UFH therapy (Grade 1C). The recommended periprocedural dosing in patients receiving a glycoprotein (GP) IIb/IIIa inhibitor is 50 to 70 U/kg (target activated clotting time [ACT] > 200 s); in patients not receiving a GP IIb/IIIa inhibitor, the recommended periprocedural dosing is 60 to 100 U/kg (target ACT, 250 to 350 s).

2.5 Low-Molecular-Weight Heparin

2.5.1. For patients with acute STE MI, regardless of whether or not they receive reperfusion therapy, we recommend the use of reviparin over no therapy (Grade 1B). Recommended dosing for reviparin is 3,436 IU for < 50 kg, 5,153 IU for 50 to 75 kg, or 6,871 IU for > 75 kg q12h SC up to 7 days. For patients undergoing primary PCI, UFH should be used periprocedurally and reviparin initiated 1 h after sheath removal.

2.5.2. For patients with acute STE MI receiving fibrinolytic therapy who have preserved renal function (≤ 2.5 mg/dL [220 μmol/L] in male patients and < 2.0 mg/dL [175 μmol/L] in female patients), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A). Recommended dosing for enoxaparin is for age < 75 years, 30-mg IV bolus followed by 1 mg/kg SC q12h (maximum of 100 mg for the first two SC doses); and for age ≥ 75 years, no IV bolus, 0.75 mg/kg SC q12h (maximum of 75 mg for the first two SC doses).

2.6 Fondaparinux

2.6.1. For patients with acute STE MI and not receiving reperfusion therapy, we recommend fondaparinux over no therapy (Grade 1A). Recommended dosing for fondaparinux is 2.5 mg IV for the first dose and then SC qd up to 9 days.

2.6.2. For patients with acute STE MI receiving fibrinolytic therapy and thought not to have an indication for anticoagulation, we recommend fondaparinux over no therapy (2.5 mg IV for the first dose and then SC qd up to 9 days) [Grade 1B].

2.6.3. For patients with acute STE MI receiving fibrinolytic therapy and thought to have an indication for anticoagulation, we suggest fondaparinux (2.5 mg IV for the first dose and then SC qd up to 9 days) could be used as an alternative to UFH (Grade 2B).

2.6.4. For patients with acute STE MI and undergoing primary PCI, we recommend against using fondaparinux (Grade 1A).

2.7 Direct Thrombin Inhibitors

2.7.1. For patients with acute STE MI treated with streptokinase, we suggest clinicians not use bivalirudin as an alternative to unfractionated heparin (Grade 2B).

Underlying values and preferences: This recommendation places a relatively higher value on avoiding excess of major bleeding and a relatively lower value on avoiding reinfarction. Recommended dosing for bivalirudin is 0.25 mg/kg IV bolus followed by an infusion of 0.5 mg/kg/h for the first 12 h and then 0.25 mg/kg/h for the subsequent 36 h; APTTs should be measured at 12 h and 24 h with potential dose reductions as noted (see Section 2.7. below).

2.8 GP IIb/IIIa Inhibitors

2.8.1. For patients with acute STE MI, we recommend against the combination of standard-dose abciximab and half-dose reteplase or tenecteplase with low-dose IV UFH over standard-dose reteplase or tenecteplase (Grade 1B).

2.8.2. For patients with acute STE MI, we suggest clinicians not use the combination of streptokinase and any GP IIb/IIIa inhibitor (Grade 2B).

2.8.3. For patients with acute STE MI undergoing primary PCI (with or without stenting), we
recommended the use of abciximab (Grade 1B). Recommended dosing for abciximab is 0.25 mg/kg IV bolus followed by 0.125 μg/kg/min (maximum, 10 μg/min) for 12 h.

3.0 Facilitated PCI

3.0.1. For patients with acute STE MI undergoing primary PCI, we recommend against the use of fibrinolysis, with or without a GP IIb/IIIa inhibitor (Grade 1B).

3.0.2. For patients with acute STE MI who are to undergo primary PCI, we suggest administration of a GP IIb/IIIa inhibitor prior to coronary angiography (Grade 2B). The largest number of patients studied in this setting received abciximab, 0.25 mg/kg IV bolus, followed by 0.125 μg/kg/min (maximum, 10 μg/min) for 12 h; recommended dosing for eptifibatide is two 180 μg IV boluses (10 min apart) followed by 2.0 μg/kg/min infusion for 12 to 24 h; recommended dosing for tirofiban is 25 μg/kg IV bolus followed by 0.15 μg/kg/min for 24 h.

4.0 Rescue PCI

4.0.1. For patients with STE MI who have received fibrinolysis but who have persistent STE (< 50% resolution 90 min after treatment initiation compared with the pretreatment ECG), we recommend rescue PCI should be performed over repeat fibrinolysis or no additional reperfusion therapy (Grade 1B), and suggest as soon as possible and within 2 h of identification of lack of STE resolution (Grade 2C).

A c u t e ST-segment elevation (STE) myocardial infarction (MI) is caused by coronary plaque disruption with exposure of substances that promote platelet activation, adhesion, and aggregation, thrombin generation, and thrombus formation leading to an occluded epicardial infarct-related artery (IRA).1 Antiplatelet and antithrombotic therapy should be administered to all patients with an acute coronary syndrome (ACS). Patients presenting with persistent STE should also be considered for timely reperfusion therapy (either pharmacologic or catheter-based) in order to restore coronary flow and limit myocardial necrosis. This review will focus mainly on approved agents and the randomized trials that have led to their widespread utilization. Table 1 describes the question definition and eligibility criteria for the studies considered in each section of the article. It is important to note that the grades of recommenda-

1.0 Reperfusion Therapy

Among patients with persistent STE, prompt and complete restoration of flow in the IRA can be achieved with either a pharmacologic (fibrinolysis) or catheter-based (percutaneous coronary intervention [PCI]), pharmacologically supported approach. Regardless of the reperfusion strategy employed, there is strong evidence supporting restoration of IRA flow in a rapid time frame.1–5 Indeed, the optimal goal of any local medical system is to facilitate rapid recognition and treatment of patients with STE MI such that medical contact-to-needle (or door-to-needle) time for initiation of fibrinolytic therapy can ideally be achieved within 30 min or that medical contact-to-balloon (or door-to-balloon) time for PCI majority of patients within 90 min.6

Reperfusion with primary PCI has emerged as an extremely effective method for re-establishing IRA patency and is suitable for at least 90% of patients.7–9 When performed by experienced operators in optimal settings, successful TIMI-3 flow can be achieved in 80 to 95% of cases.10–14 Primary PCI has been compared with fibrinolysis in > 20 randomized clinical trials of patients with STE MI, and an overview9 demonstrated that patients undergoing PCI compared with fibrinolytic treatment had significantly lower short-term mortality rates (5% vs 7%; odds ratio [OR], 0.70; 95% confidence interval [CI], 0.58 to 0.85; p = 0.038), nonfatal MI (3% vs 6%; OR, 0.42; 95% CI, 0.31 to 0.55), and ICH (0.05% vs 1.0%; OR, 0.05; 95% CI, 0.006 to 0.35; p < 0.0001). There was an increased risk for major bleeding in patients undergoing primary PCI (7% vs 5%; OR, 1.3; 95% CI, 1.02 to 1.65; p = 0.032). The mortality benefit was present in trials testing streptokinase as well as in studies using fibrin-specific agents. The short-term benefits of primary PCI over fibrinolytic therapy appear to be sustained.15–17

There is substantial debate, however, regarding the timing of primary PCI relative to symptom onset and hospital presentation; for example, one analysis16 of randomized controlled trials that compared primary PCI with fibrin-specific lytic agents suggested that the mortality benefit with PCI was only evident when treatment was delayed by no more than 60 min, while another study19 found that primary PCI was associated with signif-
Significantly lower 30-day mortality regardless of treatment delay. Further, the ongoing investigation and availability of new agents, dosing regimens, devices, adjunctive treatments, and combinations is a dynamic process. Thus, the selection of reperfusion strategy remains controversial and is beyond the scope of these clinical practice guidelines; instead, the focus of this chapter is on antithrombotic therapy, including fibrinolysis. Further, despite the proven benefits of primary PCI, fibrinolytic therapy will continue to have a pivotal role in reperfusion therapy. This is because access to timely\textsuperscript{20} and optimal\textsuperscript{21,22} primary PCI is limited both in the United States and worldwide. In contrast, fibrinolytic therapy is available universally and can be administered in a timely manner by community and emergency physicians. Although most evaluations of PCI have been in patients who are eligible to receive fibrinolysis, there may be substantial value of PCI in patients who may not be suitable for fibrinolytic therapy because of an increased risk of bleeding.\textsuperscript{23} While there are no randomized controlled trials evaluating the outcome of PCI for patients who present with STE MI but who are ineligible for fibrinolytic therapy, these patients are at increased risk for mortality.\textsuperscript{24} and it has been suggested that PCI be considered for achieving reperfusion in these patients.\textsuperscript{23,25,26}

### 1.0 Reperfusion Therapy

#### Recommendation

1.0.1. For patients with ischemic symptoms characteristic of acute MI of $\leq 12$ h in duration and persistent STE, we recommend that all undergo rapid evaluation for reperfusion (primary PCI or fibrinolytic) therapy and have a reperfusion strategy implemented promptly after contact with the health-care system (Grade 1A).

### Table 1—Question Definition and Eligibility Criteria (Section: Intro)\textsuperscript{*}

<table>
<thead>
<tr>
<th>Section</th>
<th>Population</th>
<th>Intervention or Exposure/Comparison</th>
<th>Outcomes</th>
<th>Methodology</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Reperfusion therapy</td>
<td>Acute STE MI</td>
<td>Streptokinase, tPA, antistreplase, reteplase, and tenecteplase compared against each other or with placebo</td>
<td>Patency of IRA; mortality, recurrent ischemia, ICH, severe or major bleeding</td>
<td>RCT</td>
<td>None</td>
</tr>
<tr>
<td>2.0 Antiplatelet/antithrombotic therapy</td>
<td>Acute STE MI with or without reperfusion therapy</td>
<td>Aspirin compared to other antiplatelet therapy or placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
</tr>
<tr>
<td>2.1 Acute STE MI with or without reperfusion therapy</td>
<td>Clopidogrel compared to placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.2 Acute STE MI with or without reperfusion therapy</td>
<td>Antithrombin therapy compared to placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.3 Acute STE MI with or without reperfusion therapy</td>
<td>UHF compared to placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.4 Acute STE MI with or without reperfusion therapy</td>
<td>LMWH compared to placebo or UFH</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.5 Acute STE MI with or without reperfusion therapy</td>
<td>Fondaparinux compared to UFH or placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.6 Acute STE MI with or without reperfusion therapy</td>
<td>Direct thrombin inhibitors compared to placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2.7 Acute STE MI with or without reperfusion therapy</td>
<td>GP IIb/IIIa inhibitors compared to placebo</td>
<td>Death, recurrent MI, ICH, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>3.0 Facilitated PCI</td>
<td>Acute STE MI</td>
<td>Fibrinolysis and/or GP IIb/IIIa inhibitors followed by immediate PCI compared against fibrinolysis or primary PCI</td>
<td>Death, recurrent MI, ICH, cardiogenic shock, heart failure, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
</tr>
<tr>
<td>4.0 Rescue PCI</td>
<td>Acute STE MI receiving fibrinolysis</td>
<td>Rescue PCI compared to no treatment or repeat fibrinolysis</td>
<td>Death, recurrent MI, ICH, severe CHF, severe/major bleeding</td>
<td>RCT</td>
<td>None</td>
</tr>
</tbody>
</table>

\textsuperscript{*RCT} = randomized controlled trial; CHF = congestive heart failure.
1.1 Fibrinolysis

More than 150,000 patients have been randomized in trials of fibrinolytics vs placebo/control, or one fibrinolytic regimen compared with another.27–41 For patients treated within 12 h of symptom onset, the overall evidence for the benefit of fibrinolytic therapy is overwhelming. The Fibrinolytic Therapy Trialists (FTT) analysis42—a collaborative overview of early mortality and major morbidity results from nine trials27–34 of fibrinolysis vs control that randomized > 1,000 patients with suspected MI each (n = 58,600)—described approximately 18 fewer deaths per 1,000 patients treated (Tables 2, 3). These mortality benefits were evident despite an excess of deaths during days 0 to 1 (especially among patients presenting > 12 h after symptom onset, and in the elderly); this “early hazard” was far outweighed by a much larger benefit during days 2 to 35. Benefit was observed among patients presenting with STE or bundle-branch block (BBB), irrespective of age, sex, BP (if < 150 mm Hg systolic), heart rate, or previous history of MI or diabetes.42 The mortality benefit was remarkably consistent across prestratified subgroups; hence, the largest absolute benefit is seen among patients with the highest risk.

The absolute survival benefit in patients > 75 years of age and treated within 24 h was small and not statistically significant; further, two nonrandomized, observational analyses45,46 questioned the benefit of fibrinolytic therapy in the elderly, with one of these studies45 suggesting more harm than good. However, a reanalysis by the FTT secretariat indicates that in approximately 3,300 patients over the age of 75 years presenting within 12 h of symptom onset and with either STE or BBB, mortality rates were significantly reduced by fibrinolytic therapy (from 29.4% to 26%, p = 0.03).47 Another nonrandomized, observational study48 in 6,891 patients ≥ 75 years old with first registry-recorded STE MI also confirm an overall survival advantage to fibrinolysis in the elderly.

Several randomized trials49–54 of prehospital-initiated fibrinolysis have provided important insights regarding the impact of early treatment (Tables 4, 5). Indeed, acquisition of 12-lead ECGs in the field and the use of a reperfusion checklist (Fig 1)6 could lead to more rapid prehospital and hospital care.54,55 Although none of the individual trials demonstrated an early mortality reduction with prehospital-initiated fibrinolysis, a metaanalysis (performed prior to the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial56) of six trials (n = 6,434) demonstrated a significant reduction in all-cause hospital mortality (OR, 0.83; 95% CI, 0.70 to 0.98; p = 0.03).57 These findings were associated with a significantly earlier treatment of patients in the prehospital-treated group when compared to a convention in-hospital strategy (mean, 104 min vs 162 min; p = 0.007) The Grampain Region Early Anistreplase Trial,51 included in the metaanalysis,57 did find a dramatic reduction in 1-year mortality (10.4% vs 21.6%; relative risk reduction [RRR] 52%; 95% CI, 14 to 89%; p = 0.007) among patients randomized within 4 h of symptom onset (n = 311) to prehospital lysis by their general practitioner compared to in-hospital fibrinolysis; this mortality difference was seen in the context of a median 130 min earlier administration of fibrinolytic treatment.58 In the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial,56 patients randomized within 2 h of symptom onset (n = 460) had a trend toward lower 30-day mortality with prehospital fibrinolysis compared to those receiving primary PCI (2.2% vs 5.7%, p = 0.058). Similarly, patients in the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis trial50 who were randomized within 3 h of symptom onset (n = 551) had similar mortality rates whether treated by fibrinolysis or primary PCI (7.4% vs 7.3%).

Utilization of bolus fibrinolytic therapy may enhance further the feasibility of prehospital fibrinolysis. In the Early Retavase-Thrombolysis in Myocardial Infarction 19 study,61 utilization of prehospital reteplase decreased the time to initial treatment by 32 min compared to conventional in-hospital administration. As a result, 49% of patients received initial therapy within 30 min of first medical contact compared to only 5% in the standardly treated group (p < 0.0001). Similarly, the combination of tenecteplase and enoxaparin utilized as a prehospital strategy enabled 53% of patients to receive reperfusion therapy within 2 h in the ASSENT-3 PLUS trial.62

Thus, systems with experience with prehospital fibrinolysis, including a well-integrated mechanism for obtaining and transmitting a 12-lead ECG, show excellent short- and long-term mortality results. For example, data (n = 1,922) from a national registry55 in France (with physician attendance in the ambulance) suggest that the lowest in-hospital and 1-year mortality rates from STE MI were in those patients receiving prehospital lysis (n = 180) compared with patients receiving in-hospital fibrinolysis or primary PCI (3.3% vs 8% vs 6.7%; p < 0.05; and 6% vs 11% vs 11%, respectively). In a multivariable analysis of predictors of 1-year survival, prehospital lysis was associated with a lower relative risk of death (relative risk [RR], 0.49; 95% CI, 0.24 to 1.00; p = 0.05),
Table 2—Large (>1,000 Patients) Randomized Trials of IV Fibrinolytic Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 1.1)*

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Entry ECG Features</th>
<th>Time From Symptom Onset to Randomization, h (%)</th>
<th>Fibinolytic Regimen</th>
<th>Control</th>
<th>Routine Antiplatelet</th>
<th>Routine Heparin, Dose, Duration</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total Patients (%); RR (95% CI) Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-127</td>
<td>STE 91 BBB 1 ST-segment depression 4 Other 5 Normal 0</td>
<td>0–6 (83); 7–12 (17)</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h</td>
<td>Open</td>
<td>No</td>
<td>No</td>
<td>35</td>
<td>Streptokinase: 628/5,860 (10.7) Control: 758/5,852 (13.0); 0.81 (0.72–0.90)</td>
</tr>
<tr>
<td>ISAM28</td>
<td>STE 94 BBB 5 ST-segment depression 0 Other 1 Normal 0</td>
<td>0–6 (100)</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h</td>
<td>Placebo</td>
<td>Aspirin (single IV bolus)</td>
<td>Yes, IV 5,000 U + 800–1,000 U/h for 72–96 h, then oral anticoagulant</td>
<td>21</td>
<td>Streptokinase: 548/59 (6.3) Placebo: 63/882 (7.1); 0.88</td>
</tr>
<tr>
<td>AIMS39</td>
<td>STE 99 BBB 0 ST-segment depression 1 Other 0 Normal 0</td>
<td>0–6 (100)</td>
<td>APSAC 30 U over 5 min</td>
<td>Placebo</td>
<td>No</td>
<td>Yes, IV 1,000–1,500 U/h starting 6 h post-lysis, until effective oral anticoagulation</td>
<td>30</td>
<td>APSAC: 32/502 (6.4) Placebo: 61/502 (12.2) 0.53 (0.35–0.79)</td>
</tr>
<tr>
<td>ISIS-291</td>
<td>STE 61 BBB 4 ST-segment depression 7 Other 25 Normal 2</td>
<td>0–6 (63); 7–12 (23); 13–24 (14)</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h</td>
<td>Placebo</td>
<td>Aspirin (50%)</td>
<td>No</td>
<td>35</td>
<td>Streptokinase: 1791/8,592 (20.2) Placebo: 11,029/8,395 (12.0) OR 25% SD 4%</td>
</tr>
<tr>
<td>ASSET100</td>
<td>STE BBB 4 ST-segment depression, or Other 82 Normal 18</td>
<td>0–6 (100)</td>
<td>tPA 100 mg over 3 h</td>
<td>Placebo</td>
<td>No</td>
<td>Yes, IV 5,000 U + 1,000 U/h for 24 h</td>
<td>30</td>
<td>tPA: 182/2,516 (7.2) Placebo: 245/2,495 (9.8); 0.74 (0.61–0.89)</td>
</tr>
<tr>
<td>USIM31</td>
<td>STE 89 BBB 0 ST-segment depression 0 Other 10 Normal 0</td>
<td>0–6 (100)</td>
<td>Urokinase 1 × 10^6 U bolus repeated at 60 min</td>
<td>Open</td>
<td>No</td>
<td>Yes, IV 10000 U + 1,000 U/h for 48 h In hospital (9–16 in &gt; 90%)</td>
<td>35</td>
<td>Urokinase: 901/1,123 (8.0) Control: 89/1,073 (8.3); 0.96 (0.70–1.31)</td>
</tr>
<tr>
<td>ISIS-332</td>
<td>STE 30 BBB 8 ST-segment depression 19 Other 25 Normal 17</td>
<td>0–6 (54); 7–12 (28); 13–24 (18)</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h or tPA 0.6 × 10^6 U/kg over 4 h or APSAC 30 U over 3 min</td>
<td>Open</td>
<td>Aspirin</td>
<td>50% SC 12S500 U bid for 7 d</td>
<td>35</td>
<td>Fibrinolytic: 4004/601 (8.7) Control: 375/4,557 (8.2) 37,000 patients considered to have &quot;certain&quot; indication for lysis and randomized between streptokinase, tPA, and APSAC not included; 9,158 patients with &quot;uncertain&quot; indication for lysis allocated to lysis (1/3 to each lytic; combined in this report) or open control</td>
</tr>
</tbody>
</table>
including when the analysis was limited to patients receiving reperfusion therapy (RR, 0.52; 95% CI, 0.25 to 1.08; p \( /H_11005 0.08\)).

In the FTT overview, among the 45,000 patients presenting with STE or BBB, the relation between benefit and delay from symptom onset indicated highly significant absolute mortality reductions of about 30 deaths prevented per 1,000 patients (by 35 days) treated within 6 hours of symptom onset. For those presenting at 7 to 12 hours, there were approximately 20 deaths prevented per 1,000 patients treated; beyond 12 hours, there was a statistically uncertain benefit of about 10 per 1,000. While the FTT overview reported an apparent linear relationship between absolute mortality benefit and time from symptom onset to treatment (1.6 deaths per hour of delay per 1,000 patients treated), another metaanalysis of 22 trials (n = 50,246) suggested a nonlinear relation.

The beneficial effect of fibrinolysis was substantially higher in patients presenting within 2 hours after symptom onset compared to those presenting later. These estimations, based on studies in which the time to treatment was not randomized, must be interpreted with caution because the time to presentation is not random. Nevertheless, they should be considered as an additional indirect support for prehospital initiation of fibrinolysis.

Although the FTT overview indicates that patients with BBB are at high risk when presenting with a presumed MI and a mortality benefit of fibrinolysis was evident (35-day mortality, 18.7% vs 23.6% in control patients; p \( /H_11021 0.01\)), there are some important caveats to consider. First, the trials included in the FTT Collaborative Group overview did not distinguish between left and right BBB. While the diagnosis of STE can usually be made without difficulty in the presence of right BBB, the presence of left BBB presents greater challenges in the determination of whether there associated ST-segment deviation is indicative of underlying occlusion of the IRA. Although some criteria have been proposed based on the GUSTO-I experience demonstrating good sensitivity and specificity for the identification of patients with MI, these were derived from a highly selected, clinical trial population.

In the Thrombolysis in Myocardial Ischemia III Registry of patients with presumed acute MI and unstable angina, acute MI was diagnosed in only 32% of the 127 patients with left BBB. In the Thrombolysis in Myocardial Ischemia III Registry of patients with presumed acute MI and unstable angina, acute MI was diagnosed in only 32% of the 127 patients with left BBB. In the Thrombolysis in Myocardial Ischemia III Registry of patients with presumed acute MI and unstable angina, acute MI was diagnosed in only 32% of the 127 patients with left BBB. In the Thrombolysis in Myocardial Ischemia III Registry of patients with presumed acute MI and unstable angina, acute MI was diagnosed in only 32% of the 127 patients with left BBB. In the Thrombolysis in Myocardial Ischemia III Registry of patients with presumed acute MI and unstable angina, acute MI was diagnosed in only 32% of the 127 patients with left BBB.

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Entry ECG Features</th>
<th>%</th>
<th>Time From Symptom Onset to Randomization, h (%</th>
<th>Fibrinolytic Regimen</th>
<th>Control</th>
<th>Routine Antiplatelet</th>
<th>Routine Heparin, Dose, Duration</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total Patients (%); RR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMERAS33</td>
<td>STE 76, BBB 6,</td>
<td></td>
<td>10–6 (4); 7–12 (46); 13–24 (40)</td>
<td>Streptokinase 1.5 ( x 10^7 ) U over 1 h</td>
<td>Placebo</td>
<td>Aspirin No</td>
<td>Placebo: 269/2,257 (11.9)</td>
<td>0.86 (0.72–1.00)</td>
<td>After ISIS-2 results became available, only patients presenting &gt; 6 h after symptom onset were randomized</td>
<td></td>
</tr>
<tr>
<td>LATE34</td>
<td>STE 55, BBB 2,</td>
<td></td>
<td>10–6 (3); 7–12 (38); 13–24 (60)</td>
<td>tPA 100 mg over 3 h</td>
<td>Placebo</td>
<td>Aspirin</td>
<td>Placebo: 397/2,836 (8.9)</td>
<td>0.86 (0.72–1.00)</td>
<td>Patients presenting ≤ 6 h after symptom onset were to be excluded</td>
<td></td>
</tr>
</tbody>
</table>

*APSAC = anisoylated plasminogen streptokinase activator complex; other = other ECG abnormalities.
†Adapted from FTT Collaborative Group.
V<sub>1</sub>–V<sub>4</sub> ST-segment depression. Indeed, those patients with suspected acute MI and left BBB but without apparent ST-segment changes had a lower mortality than patients with suspected acute MI and STE, but with normal conduction (OR, 0.52; 95% CI, 0.33 to 0.80). Thus, it remains unclear whether routine administration of fibrinolysis to all patients with suspected acute MI and left BBB is indicated; this may represent a situation in which primary PCI could be preferable to fibrinolytic therapy.

As noted above, in the absence of STE, there is no evidence of benefit of fibrinolytic therapy for patients with normal ECG or nonspecific changes, and there is some suggestion of harm (including an increased risk of bleeding) for patients with ST-segment depression only. However, fibrinolytic therapy may be appropriate when there is marked ST-segment depression confined to leads V<sub>1</sub>–V<sub>4</sub> and accompanied by tall R waves in the right precordial leads and upright T waves indicative of a
true posterior injury current and possibly circumflex coronary occlusion. Confirmation of data from posterior leads (i.e., V7–V9) as well as emergent echocardiography, if available, may offer additional information that could guide therapeutic decision making. As with left BBB, primary PCI is another reperfusion strategy that may be effective in patients with true posterior MI.

1.1.1 Safety

A detailed list of contraindications and cautions for the use of fibrinolytic therapy is shown in the Table 6. Hemorrhage represents the most important risk of fibrinolytic therapy, especially intracranial hemorrhage (ICH), which is fatal in up to two thirds of patients. The FTT42 reported an excess of 3.9 strokes per 1,000 patients treated with fibrinolysis vs placebo. The excess stroke risk associated with fibrinolytic therapy largely is attributable to the excess risk of ICH. For example, in the GUSTO-I trial37 (n = 41,021), 268 patients had an ICH, of whom 160 patients (59.7%) died by 30 days.73 Several models have been developed for estimating the risk of ICH after fibrinolysis.43,73–76 The models incorporate baseline demographic features of the patient (e.g., age, weight, hypertension on admission) and also illustrate the impact of certain therapeutic decisions (e.g., selection of streptokinase vs tissue plasminogen activator [tPA]).

### Table 6—Contraindications and Cautions for Fibrinolysis in STE MI (Section 1.1.1)*

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior ICH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known structural cerebral vascular lesion (e.g., arteriovenous malformation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known malignant intracranial neoplasm (primary or metastatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke within 3 mo except acute ischemic stroke within 3 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding or bleeding diathesis (excluding menses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant closed-head or facial trauma within 3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative contraindications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of chronic, severe, poorly controlled hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe uncontrolled hypertension on presentation (systolic BP &gt; 180 mm Hg or diastolic BP &gt; 110 mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of prior ischemic stroke &gt; 3 mo, dementia, or known intracranial pathology not covered in contraindications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic or prolonged (&gt; 10 min) cardiopulmonary resuscitation or major surgery (≥ 3 wk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (≤ 2–4 wk) internal bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncompressible vascular punctures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For streptokinase/anistreplase: prior exposure (&gt; 5 days ago) or prior allergic reaction to these agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active peptic ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of vitamin K antagonists: the higher the international normalized ratio, the higher the risk of bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive. Adapted from Antman et al.6

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Figure 1. Reperfusion checklist for evaluation of the patient with STE MI. From Antman et al6 (Reprinted with permission ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction, 2004, American Heart Association, Inc.).
The dosage of adjunctive IV unfractionated heparin (UFH), the measured activated partial thromboplastin time (APTT) level as well as the timing of APTT monitoring appears to have a strong relationship with the risk of ICH.77,78 Three trials, TIMI-9A,79 GUSTO-Ia,80 and TIMI 10B,81 reduced the initial protocol-recommended heparin dosage during the course of the study because of early observations of excessive rates of hemorrhage. The subsequent results of these trials indicated a decline in the rate of ICH: TIMI-9B82 (1.87 to 1.07%), GUSTO-Ib83 (0.92 to 0.71%), and TIMI 10B83 (2.8 to 1.16%). More recent trials like ASSENT-2,41 ASSENT-3,84 InTIME-II,85 and ExTRACT-TIMI 2586 all employed reduced-dose heparin regimens with bolus fibrinolytic drugs. Timing of the APTT as well as the intensity appears to influence the risk of ICH. Early trials recommended initial APTT evaluation at 6 h; however, the InTIME-II trial85 evaluated heparin dose adjustment with 3-h APTT monitoring. This was associated with the lowest reported ICH rate of 0.64% observed in any megatrial, and when this approach was undertaken in the ASSENT-3 trial,84 the heparin dosing regimen resulted in a 0.94% ICH rate (see section on heparin).

There remains significant uncertainty surrounding the issue of whether fibrinolysis should be contraindicated in patients with a history of prior cerebrovascular disease.6 This stems, in part, from the fact that in many trials, the use of prior transient ischemic attack or stroke as an exclusion criterion has varied. In the prospective, observational German Myocardial Infarction Registry and Maximal Individual Therapy in Acute Myocardial Infarction registries, previous stroke within 3 months was the strongest predictor of stroke (OR, 9.3; 95% CI, 6 to 14.2) after STE MI.87 Similarly, in the prospective, observational FASTRAK II registry, a previous cerebrovascular event (stroke or transient ischemic attack) was an independent predictor of ICH (OR, 2.4; 95% CI, 1.3 to 4.7).88 In patients with prior ischemic stroke and other ICH risk factors, primary PCI should be considered as an alternative to fibrinolysis.

In addition to stroke and ICH, the FTT Collaborative Group42 defined major bleeding events as those that were considered life-threatening or required blood transfusion, and reported a 1.1% incidence among patients receiving fibrinolytic therapy compared with 0.4% (p < 0.00001) among those receiving placebo, an increase of seven major bleeds per 1,000 patients so treated. In a comprehensive report on noncerebral bleeding after fibrinolytic therapy, Berkowitz et al89 defined severe bleeding as that causing substantial hemodynamic compromise requiring intervention, and moderate bleeding as that requiring transfusion but without associated hemodynamic compromise. tPA plus IV UFH was associated with numerically lower rates of moderate or severe, or severe bleeding (0.9%) when compared to streptokinase (with subcutaneous [SC] UFH, 1.2%; or IV UFH, 1.5%). The most common cause of bleeding in GUSTO-I was associated with the use of coronary revascularization procedures. Consistent with predictors of ICH, the most powerful multivariable predictors of moderate or severe bleeding were advanced age, lighter body weight, and female gender, even among patients who did not undergo an in-hospital cardiac procedure. Together with the observation in the ASSENT-2 study41 that the even more fibrin-specific agent tenecteplase resulted in significantly less major bleeding and need for blood transfusion when compared to tPA, it appears that the choice of fibrinolytic agent may indeed impact on the risk of bleeding.

Characteristics and dosages for the current fibrinolytic agents are provided in Table 7. Some relevant, lytic-specific information and comparisons between fibrinolytics and placebo or against each other are provided below (Table 8).

1.1.2 Streptokinase

Prior to 1986, 24 randomized clinical trials of IV fibrinolytic treatment performed over a 25-year period had been reported in approximately 6,000 patients in the acute phase of MI.90 The majority of these trials involved streptokinase administered in a variety of regimes and were relatively small in number (sample sizes ranging from 23 to 747 patients). However, an overview90 of the data (n = 5,284) suggested that IV streptokinase produced a highly significant (OR, 0.78; 95% CI, 0.68 to 0.89; p < 0.001; 3.8% absolute) reduction in mortality. Several large-scale randomized trials27,91 evaluating outcomes up to 35 days after MI were subsequently published, confirming this mortality benefit. Longer-term follow-up of the first megatrial (n = 11,712), the Gruppo Italiano per lo Studio Streptokinasi nell’Infarto Miocardico study,27 demonstrated that the benefit of a single IV infusion of streptokinase realized within the first 21 days after MI (10.7% vs 13%; RR, 0.81; 95% CI, 0.72 to 0.90; p = 0.0002) was sustained out to 1 year (17.2% vs 19.0%; RR, 0.90; p = 0.00892 and 10 years,93 respectively. Similarly, the second International Study of Infarct Survival study91 demonstrated a significant reduction in 35-day vascular mortality in 17,187 patients randomized to streptokinase compared with placebo (9.2% vs 12.0%; RRR, 25%; 95% CI, 18 to 32%; p < 0.00001); this early benefit of 29 fewer deaths per 1,000 patients treated was sustained at 4
years (28 fewer deaths per 1,000 patients treated) and 10 years of follow-up (23 fewer deaths per 1,000 patients treated).94

The Estudio Multicentrico Estreptoquinasa Republicas de America del Sur trial33 was altered to include only patients who presented at least 6 h after but within 24 h of symptom onset, once the ISIS-2 results91 were reported. Mortality at 35 days did not differ significantly between the streptokinase and placebo groups in the 3,568 patients enrolled between 6 h and 24 h (11.2% vs 11.8%, p not significant).33 In the subgroup of patients (n = 2,080) enrolled 7 h and 12 h, there was a numeric but nonsignificant reduction in deaths with streptokinase (11.7% vs 13.2%; RRR, 14%; 95% CI, 33 to 12% increase).

### 1.1.3 tPA

A number of angiographic trials initially compared patency with tPA compared to streptokinase. These early trials observed that the 3-h dosing regimen of alteplase (tPA) resulted in superior patency and TIMI grade 3 flow results at both 60 min and 90 min compared with streptokinase or anistreplase.95 Neuhaus and colleagues96 developed an “accelerated,” 90-min dosing regimen for alteplase, which achieved even higher rates of early reperfusion than did the 3-h regimen of alteplase,97 anistreplase treatment,98,99 or streptokinase treatment.100 Given the importance of rapid reperfusion, a fibrinolytic regimen that achieves a higher rate of early IRA patency was expected to be associated with lower mortality. However, findings from larger clinical trials evaluating clinical outcome did not initially support this hypothesis. The large Gruppo Italiano per lo Studio Sopravvivenza nell’Infarto Miocardico 235/International Study Group36 included patients (n = 20,981) with STE randomized within 6 h of symptom onset and found no differences in hospital mortality between tPA and streptokinase (8.9% vs 8.5%). While more strokes were reported with tPA (1.3% vs 1%), more major bleeds occurred with streptokinase (0.6% vs 0.9%). Patients were also randomly allocated to SC UFH, beginning 12 h after the start of fibrinolytic therapy, or no UFH. Again, no differences in hospital mortality were evident (8.5% vs 8.9%), but SC heparin was associated with an excess of major bleeds (1.0% vs 0.5%) and did not affect the incidence of stroke or reinfarction. Six-month follow-up also demonstrated similar mortality rates in the tPA and streptokinase groups (12.3% vs 11.7%; RR, 1.06; 95% CI, 0.97 to 1.15), and the SC UFH and no UFH groups (11.9% vs 12.1%; RR, 0.98; 95% CI, 0.90 to 1.07).101 The ISIS-3 trial32 randomized patients (n = 41,299) within 24 h of presentation of a suspected MI, with or without ECG changes. Of note, patients for whom their physicians thought there was a “clear” indication for fibrinolytic therapy were randomized equally between streptokinase, duteplase, and anistreplase; those for whom the indication was considered “uncertain” (eg, presented > 6 h after symptom onset or had not definite STE) were randomized equally between fibrinolytic therapy (streptokinase, duteplase, or antistreplase) and open control. Similar to the GISSI-235/International Study Group36 trials, patients were also randomized to two different anti-thrombotic regimens; in ISIS-3 trial32 this consisted of a fixed-dose regimen of 12,500 IU of UFH, starting about 4 h after randomization and given SC bid for 7 days or until discharge or no UFH. In the fibrinolytic comparison, mortality rates at 35 days (10.6% vs

### Table 7—Characteristics of IV Fibrinolytic Agents (Section 1.1.1)*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Fibrin Specific Metabolism</th>
<th>Half-Life, min</th>
<th>Mode of Action</th>
<th>Allergic Reactions</th>
<th>Dosing</th>
<th>Hospital Cost/Dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>—</td>
<td>18–23</td>
<td>Activator complex</td>
<td>Yes</td>
<td>1.5 × 10^6 U over 60 min</td>
<td>$613</td>
</tr>
<tr>
<td>Alteplase, duteplase (tPA)</td>
<td>++</td>
<td>3–8</td>
<td>Direct</td>
<td>No</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min)</td>
<td>$2,974</td>
</tr>
<tr>
<td>Reteplase</td>
<td>+</td>
<td>15–18</td>
<td>Direct</td>
<td>No</td>
<td>10 × 10^6 U × 2 boluses each over 2 min given 30 min apart</td>
<td>$2,750</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>+++</td>
<td>18–20</td>
<td>Direct</td>
<td>No</td>
<td>30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg</td>
<td>$2,8331</td>
</tr>
</tbody>
</table>

*Adapted from Antman et al.6
†Costs list current US prices of usual dose based on Mosby’s Drug Consult 2004, 8th ed.6
‡For 50 mg.
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Entry ECG Features %</th>
<th>Time from Symptom Onset to Randomization, h (%)</th>
<th>Fibrinolytic Regimens</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Routine Heparin, Dose, Duration</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI-235 1990</td>
<td>STE 100 0–6 (100)</td>
<td>3.5-10^6 U over 30–60 min tPA 100 mg over 3 h</td>
<td>Streptokinase 3.5–10^6 U over 30–60 min tPA 100 mg over 3 h</td>
<td>No</td>
<td>300–325 mg/d</td>
<td>50%, SC 12,500 U bid</td>
<td>35</td>
<td>Streptokinase: 5366/6199 (8.6); tPA: 5366/6182 (9.0) Primary end point was death plus late (day 4) clinical congestive heart failure or extensive left ventricular damage (left ventricular ejection fraction ≤ 35% or ≥ 45% myocardial segments injured by echocardiography or follow-up ECG QRS score &gt; 10): 1,394/6,199 (22.5%) vs 1,428/6,182 (23.1%), RR 1.04 (95% CI 0.95–1.13) Includes 12,490 patients in the GISSI-2 trial and 8,401 patients recruited in 13 other countries (351/4,197 8.4% vs 373/4,190 8.9%)</td>
<td></td>
</tr>
<tr>
<td>ISG 38 1990</td>
<td>STE 100 0–6 (97) &gt; 6 (3)</td>
<td>3.5-10^6 U over 30–60 min tPA 100 mg over 3 h</td>
<td>Streptokinase 3.5–10^6 U over 30–60 min tPA 0.6 × 10^6 U/kg over 4 h or APSAC 30 U over 3 min</td>
<td>No</td>
<td>300–325 mg/d</td>
<td>50%, SC 12,500 U bid</td>
<td>35</td>
<td>Streptokinase: 857/10,396 (8.5); tPA: 929/10,372 (8.9); APSAC: 1,448/13,773 (10.5); no significant mortality differences between the 3 lytic regimens Includes 12,490 patients in the GISSI-2 trial and 8,401 patients recruited in 13 other countries (351/4,197 8.4% vs 373/4,190 8.9%)</td>
<td></td>
</tr>
<tr>
<td>ISIS-3 39 1992</td>
<td>STE, 77 Normal 3</td>
<td>0–6 (63) &gt; 6 (37)</td>
<td>Streptokinase 3.5–10^6 U over 1 h or tPA 0.6 × 10^6 U/kg over 4 h or APSAC 30 U over 3 min</td>
<td>No</td>
<td>162 mg/d</td>
<td>50%, SC 12,500 U starting 4 h post-randomization and then bid for 7 d or until discharge</td>
<td>35</td>
<td>Streptokinase: 1,455/13,780 (10.6); tPA: 1,418/13,746 (10.3); APSAC: 1,448/13,773 (10.5); no significant mortality differences between the 3 lytic regimens Includes 41,299 of 45,856 patients randomized to receive fibrinolytic therapy, including patients considered to have &quot;clear&quot; or &quot;uncertain&quot; indication for lysis; 12% of patients received IV, non-trial allocated heparin</td>
<td></td>
</tr>
<tr>
<td>GUSTO-I 40 1993</td>
<td>STE 100 0–6 (100)</td>
<td>3.5-10^6 U over 1 h or tPA 100 mg over 30 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or tPA (1 mg/kg [maximum 50 mg] over 1 h with 10% given as bolus) plus streptokinase (3.5 × 10^6 U over 1 h)</td>
<td>Streptokinase 3.5–10^6 U over 1 h or tPA 100 mg over 1 h</td>
<td>No</td>
<td>160–325 mg/d</td>
<td>SC 12,500 U starting 4 h post-randomization and then bid for 7 days or until discharge or IV 5,000 U + 1,000 U/h (1200 U/h for weight &gt; 80 kg), target APTT 60-85 s</td>
<td>30</td>
<td>Streptokinase + SC UFH: 3.7,976 (7.2); Streptokinase + IV UFH: /10,357 (7.4); Accelerated tPA + IV UFH: /10,344 (6.3); tPA + streptokinase + IV UFH: /10,328 (7.0); RR Accelerated tPA vs both streptokinase groups 14% (5.9%–21.3%) Streptokinase patients randomized to receive either SC or IV UFH, tPA and combination tPA + streptokinase patients to receive IV UFH</td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>ECG Features</td>
<td>Time from Symptom Onset to Randomization, h (%)</td>
<td>Fibrinolytic Regimens</td>
<td>Blinded</td>
<td>Routine Aspirin Dose</td>
<td>Routine Heparin, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>COBALT40</td>
<td>STE 100</td>
<td>0–6 (100)</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or tPA 50 mg bolus over 1–3 min followed by 50 mg bolus (40 mg if weight &lt; 60 kg) 30 min later</td>
<td>No</td>
<td>80–325 mg/d (minimum initial 160 mg dose)</td>
<td>IV 5,000 U + 1,000 U/h (1,200 U/h for weight &gt; 80 kg), target APTT 60–85 s</td>
<td>30</td>
<td>80–325 mg/d (minimum initial 160 mg dose)</td>
<td>Mortality difference exceeds prespecified boundary of 0.40; equivalence not met</td>
</tr>
<tr>
<td>INJECT81</td>
<td>STE 98 BBB 2</td>
<td>0–6 (80) 7–12 (20)</td>
<td>Streptokinase: 1.5 × 10^6 U over 1 h or reteplase 10 × 10^6 U boluses given 30 min apart</td>
<td>Yes</td>
<td>75–150 mg/d (250–320 mg initial dose)</td>
<td>IV 5,000 U + 1,000 U/h starting 60 min post-lysis for ≥ 24 h, target APTT 1.5–2 times normal</td>
<td>35</td>
<td>Streptokinase: 285/3,006 (9.53) Reteplase: 270/3,004 (9.02) Absolute difference 0.51% (90% CI −1.76%, +0.71%)</td>
<td>Mortality difference within prespecified boundary; equivalence met</td>
</tr>
<tr>
<td>GUSTO-III</td>
<td>STE 96 BBB 3</td>
<td>0–6 (100)</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or reteplase 10 × 10^6 U boluses given 30 min apart</td>
<td>No</td>
<td>160–325 mg/d (160 mg initial dose)</td>
<td>IV 5,000 U + 1,000 U/h (800 U/h for weight &lt; 80 kg), target APTT 50–70 s</td>
<td>30</td>
<td>tPA: 4921 (7.24) Reteplase: 10138 (7.47) OR 1.03 (0.91–1.18)</td>
<td>Mortality difference within prespecified boundary; equivalence met</td>
</tr>
<tr>
<td>ASSENT-II</td>
<td>STE 95 left BBB 5</td>
<td>0–6 (100)</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or tenecteplase 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg</td>
<td>Yes</td>
<td>150–325 mg/d</td>
<td>IV 4,000 U + 500 U/h for weight ≤ 67 kg and IV 5,000 U + 1000 U/h for weight &gt; 67 kg, target APTT 50–75 s for 48–72 h</td>
<td>30</td>
<td>tPA: 8,486 (6.151) Tenecteplase: 8,461 (6.179) Absolute difference + 0.025 (95% CI −0.354–0.669)</td>
<td>Mortality difference within prespecified boundary; equivalence met</td>
</tr>
</tbody>
</table>

*See Table 2 for expansion of abbreviation.
10.3% vs 10.5%) and 6 months were similar in the streptokinase, duteplase, and antistreplase groups, respectively. Even in the prespecified subgroup of patients presenting within 6 h of symptom onset and with STE, 35-day mortality rates were not significantly different (10% vs 9.6% vs 9.9%). Compared to streptokinase, there were 5 per 1,000 fewer reinfarctions with duteplase (3.3% vs 2.8%, \( p < 0.005 \)) but 4 per 1,000 more strokes (1.0% vs 1.4%, \( p < 0.001 \)), with half of this excess due to fatal stroke. Combining the mortality data in the GISSI-2,35 International Study Group,36 and ISIS-332 trials, there was no significant difference in 6-month survival when comparing streptokinase and duteplase/alteplase (10% vs 10%).32

In contrast, to these findings, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries investigators37 (\( n = 41,021 \) presenting within 6 h of symptom onset with STE MI) demonstrated that mortality at 30 days was significantly lower in an accelerated alteplase arm compared with streptokinase (with SC UFH [12,500 U q12h beginning 4 h after the start of lysis] or IV UFH [5,000 U bolus followed by 1,000 U/h]) or a combination alteplase/streptokinase with IV UFH regimen (6.3% vs 7.2% [streptokinase and SC UFH] vs 7.4% [streptokinase and IV UFH] vs 7% [alteplase/streptokinase combination and IV UFH]; 1% absolute; 14% relative reduction; 95% CI, 5.9 to 21.3%, \( p = 0.001 \) vs the two streptokinase-only strategies). The improvement in mortality was present within the first 24 h after treatment began, with alteplase-treated patients having a significantly lower mortality rate (2.3% vs 2.8% vs 2.9% vs 2.8%; \( p = 0.005 \) for alteplase vs the two streptokinase-only strategies). For each of the streptokinase arms, 0.5% of patients suffered an ICH, compared with 0.7% of patients treated with accelerated alteplase and 0.9% of patients treated with combination fibrinolytic therapy. Thus both accelerated alteplase and IV UFH and combination alteplase/streptokinase were associated with a significant excess of hemorrhagic strokes. To put the results in perspective, the GUSTO-I investigators37 developed the concept of “net clinical benefit”: the avoidance of either death or nonfatal, disabling stroke. When comparing the net clinical benefit among the four regimens, accelerated alteplase still provided a clear benefit compared with the other three regimens. These findings at 30 days were sustained at 1-year follow-up,102 and represent a saving of 10 lives per 1,000 patients treated with accelerated alteplase vs streptokinase and SC or IV UFH.

In an angiographic substudy,100 patients (\( n = 2,431 \)) were randomized to undergo angiography at 90 min, 180 min, 24 h, or 5 days. At the 90-min time point, the alteplase-treated patients had both a significantly higher IRA patency rate and TIMI grade 3 (normal) flow. At the other three time points, there were no significant differences between the four fibrinolytic regimens; thus the benefit of accelerated alteplase37 was associated with early opening of the IRA. The improved patency at 90 min was associated with improved survival at 24 h, 30 days, and 2 years, emphasizing the benefit of rapid reperfusion.103,104 Similar findings of superior rates of IRA patency and TIMI grade 3 flow were demonstrated in another trial99 comparing accelerated alteplase, anistreplase, and their combination (all patients received IV UFH).

The benefits of accelerated alteplase seen in the GUSTO-I100 and TIMI-499 angiographic trials and the superior outcome in the GUSTO-I trial37 vs the lack of mortality benefit seen in GISSI-235/International Study Group36 and ISIS-332 trials likely reflects two factors: the alteplase regimen and the UFH dosing. The former trials used an accelerated alteplase regimen, which results in a higher rate of early patency compared with the older, 3-h regimen,95 and early, IV UFH, which improves late infarct-artery patency. In contrast, the GISSI-235/International Study Group36 and ISIS-332 trials used a slower infusion of alteplase or duteplase and delayed SC UFH. Reocclusion of an open IRA, often silent, occurs most often in this early time period and is associated with a threefold increase in mortality.105,106 Thus, a slower infusion of alteplase and delayed heparin administration could account for the apparent lack of benefit in the GISSI-235/International Study Group36 and ISIS-332 trials.

The Late Assessment of Thrombolytic Efficacy study34 included patients (\( n = 5,711 \)) presenting with a variety of ECG changes (including STE) and between 6 to 24 h from symptom onset. Mortality at 35 days was nonsignificantly lower in the alteplase (nonaccelerated administration) compared with the placebo group (8.9% vs 10.3%, \( p = 0.07 \)); however, in the prespecific analysis according to treatment within 12 h of symptom onset, there was a significant reduction in mortality in favor of alteplase (8.9% vs 12%: RR, 26%; 95% CI, 6 to 45%; \( p = 0.023 \)). Thus, in contrast to the above mentioned EMERAS trial33 (with streptokinase), but consistent with the larger GISSI-127 and ISIS-231 trials (with streptokinase), alteplase was superior to placebo, at least within the 6 to 12 h from symptom-onset window.

### 1.1.4 Double-Bolus Alteplase

A double-bolus regimen of alteplase (two 50-mg boluses administered 30 min apart) was investigated in an angiographic study,107 but TIMI grade 3 flow
was less than that seen in the accelerated alteplase group. Further, the Continuous Infusion vs Double-Bolus Administration of Alteplase trial (n = 7,169) was terminated early because of concern about the safety of the double-bolus regimen. Thirty-day mortality tended to be higher in the double-bolus group than in the accelerated-infusion group (7.98% vs 7.53%) and the upper limit of the 95% CI exceeded the prespecified limit for equivalence (0.4% difference). Thus, based on these criteria double-bolus alteplase was not equivalent to the accelerated alteplase infusion regimen. Rates of ICH were numerically, but not statistically significantly higher with double-bolus alteplase compared with an accelerated infusion of alteplase (1.12% vs 0.81%, p = 0.23). Based on these data, double-bolus alteplase is not recommended for general clinical use, and the accelerated, 90-min infusion remains the current standard dosing for alteplase treatment of STEMI.

1.1.5 Reteplase

The International Joint Efficacy of Comparison of Thrombolytic study examined whether double-bolus reteplase was at least equivalent to streptokinase in reducing mortality. The 35-day mortality rate with reteplase was 9.02% compared with 9.53% for streptokinase. The 90% CIs for the absolute mortality difference (−0.51%; 90% CI, −1.74 to 0.73%), did not extend beyond the prespecified limit for equivalence of 1%-higher mortality rate with reteplase compared with streptokinase. Even the 95% CI for the absolute mortality difference did not extend beyond 1% (−0.51%; 95% CI, −1.98 to 0.96%), suggesting that reteplase is equivalent to streptokinase and therefore superior to placebo. Six-month mortality rates were 11.02% for reteplase and 12.05% for streptokinase (absolute difference, −1.03%; 95% CI, −2.65 to 0.59%). There was a small, nonsignificant excess of in-hospital strokes in the reteplase group compared with the streptokinase group (1.23% vs 1.00%); however, the combined end point rates of death by 35 days plus continuing disability from an in-hospital stroke were not different (9.19% vs 9.79%; absolute difference, −0.61%; 95% CI, −2.09 to 0.85%).

Two angiographic studies demonstrated better TIMI grade 3 flow rates with reteplase (administered as two boluses [10 U + 10 U] 30 min apart) when compared to alteplase (using a nonaccelerated alteplase regimen in RAPID-1 and an accelerated regimen in RAPID 2). When the results of these two trials were combined, the rate of TIMI grade 3 flow at 90 min was 61% for reteplase (10 + 10 U) compared with 45% for the accelerated alteplase regimen (p < 0.01). The 16% absolute increase in TIMI grade 3 rate with reteplase over accelerated alteplase was less than the 24% increase seen with alteplase over streptokinase in the GUSTO-I angiographic substudy; however, this smaller difference translated into a much larger difference in mortality (3.1% for reteplase compared with 8.4% for alteplase) in the two RAPID trials.

The Global Use of Strategies To Open Occluded Coronary Arteries 3 study compared double-bolus reteplase with accelerated alteplase. This was a superiority trial to test whether the reported 16% increase in TIMI grade 3 flow with reteplase compared with tPA would translate into improved 30-day mortality. Patients (n = 15,059) presenting within 6 h of MI symptom onset were enrolled. The primary end point of 30-day mortality was reached in 7.47% of reteplase-treated patients and in 7.24% of alteplase-treated patients (p = 0.6). Thus, reteplase was not superior to alteplase in the GUSTO-III trial. The 95% CI for the absolute mortality difference of 0.23% ranged from 1.11% in favor of alteplase to 0.66% in favor of reteplase. Using an absolute risk difference of 1% as a cut-off for equivalence (ie, the absolute difference seen in 30-day mortality when comparing accelerated alteplase to streptokinase), these observations did not provide support for equivalence of the two agents because the 95% CI exceeded the 1% difference in favor of alteplase. The rates of stroke, bleeding, and ICH did not differ significantly. One-year follow-up results demonstrate similar mortality rates (11.06% vs 11.20%, p = 0.77; an absolute mortality difference of 0.14%; 95% CI, 1.21 to 0.93%).

1.1.6 Tenecteplase

The optimal safety and efficacy of weight-adjusted dosing of tenecteplase in combination with IV UFH was determined in the TIMI-10A, B, and the Assessment of the Safety and Efficacy of a New Thrombolytic Agent studies. Excessive rates of bleeding, including ICH, led to dosing reductions of both tenecteplase and IV UFH. After these dosing adjustments, there appeared to be comparable rates of ICH but lower rates of serious bleeding (noncerebral bleeding requiring transfusion) when compared to alteplase.

Tenecteplase was compared with accelerated alteplase in ASSENT-II, a large trial of patients (n = 16,950) with acute STEMI presenting within 6 h of chest pain onset. Overall 30-day mortality was similar between the two agents (6.17% vs 6.15%; RR, 1.00; 95% CI, 0.91 to 1.10; p value for equivalence, 0.028). Similar rates of ICH (0.93% vs 0.94%) and stroke (1.78% vs 1.66%) were also observed. Among
the group of patients at the highest risk for ICH (elderly female patients weighing ≈ 67 kg), the rate of ICH was more favorable in the tenecteplase-treated patients (1.1% vs 3.0%; multivariable adjusted OR, 0.30; 95% CI, 0.09 to 0.98; p < 0.05). Rates of major bleeding (4.7% vs 5.9%, p = 0.0002) and minor-to-moderate bleeding (26.3% vs 28.95%, p < 0.0003) and transfusions (4.25% vs 5.49%, p < 0.0002) were also lower in the tenecteplase-treated patients. At 1-year follow-up, the mortality rates remained similar (9.2% vs 9.1%).

There has been significant previous debate regarding the risk of ICH with bolus vs infusion fibrinolytic therapy. While currently recommended dosing of agents like reteplase and tenecteplase in combination with careful dosing of adjunctive antithrombotic therapy are associated with apparently reasonable rates of ICH, the concern remains that even trials involving > 15,000 patients may be underpowered to detect differences between agents when the frequency is ≤ 1%.

1.1 Fibrinolysis

Recommendations

1.1.1. In patients with acute MI who are candidates for fibrinolytic therapy, we recommend administration as soon as possible (ideally within 30 min) after arrival to the hospital or first contact with the health-care system (Grade 1A).

1.1.2. In health-care settings where prehospital administration of fibrinolytic therapy is feasible, we recommend prehospital administration of fibrinolytic therapy (Grade 1A).

1.1.3. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration and persistent STE, we recommend administration of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase over no fibrinolytic therapy (all Grade 1A).

1.1.4. For patients with symptom duration ≤ 6 h, we recommend the administration of alteplase (Grade 1A) or tenecteplase (Grade 1A), and suggest reteplase (Grade 2B) over streptokinase. (Grade 2B)

1.1.5. For patients receiving fibrinolytic therapy, we suggest the use of a bolus agent (eg, tenecteplase) to facilitate the ease of administration and potentially reduce the risk of ICH-related bleeding (tenecteplase, Grade 2A).

1.1.6. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration, and left BBB with associated ST-segment changes, we recommend fibrinolytic therapy if primary PCI is not readily available (Grade 1B).

1.1.7. For patients with ischemic symptoms characteristic of acute MI of ≤ 12 h duration and ECG findings consistent with a true posterior MI, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.8. For high-risk patients with ongoing symptoms characteristic of acute MI or hemodynamic compromise and duration of 12 to 24 h who have persistent STE or left BBB with ST-segment changes, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.9. In patients with any history of ICH, or with history of head trauma, or with ischemic stroke within the past 6 months, we recommend against administration of fibrinolytic therapy (Grade 1C).

2.0 Antiplatelet/Antithrombotic Therapy

While the initial goal of reperfusion is to restore flow in the IRA as quickly and completely as possible, the ultimate goal of reperfusion in STE MI is to maintain IRA patency and improve myocardial perfusion in the infarct zone. Despite adequate restoration of flow in the epicardial IRA, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury. Microvascular damage occurs as a consequence of downstream embolization of platelet microemboli and thrombi following by release of substances from activated platelets that promote occlusion or spasm. Thus, in order to maintain IRA patency (decreasing thrombus accretion and preventing reocclusion) and potentially minimize microvascular damage, adjunctive antiplatelet and antithrombotic treatments should be included in the management of acute STE MI, regardless of the reperfusion strategy initially employed.

Aspirin

All patients with a suspected ACS should be considered for aspirin treatment unless they have documented serious allergic reaction, recent severe GI bleeding, or suspected ICH. Treatment should be initiated as early as possible, at the time of initial contact with health-care personnel. The dramatic benefit of aspirin administration was established by the landmark ISIS-2 trial (described previously). Treatment with 162.5 mg/d of enteric-coated aspirin for 1 month (first tablet crushed, sucked, or chewed) produced a highly significant reduction in 5-week vascular mortality (9.4% vs 11.8%; OR, 23%; 95% CI, 15 to 30%; p < 0.00001). In addition to the 23
lives saved per 1,000 patients treated, treatment with aspirin also prevented 10 nonfatal reinfarctions and 3 nonfatal strokes per 1,000 patients treated. When aspirin was combined with streptokinase, the mortality benefit was significantly better than either agent alone.

A metaanalysis\textsuperscript{121} including the ISIS-2 trial\textsuperscript{91} and 14 other trials (n = 19,288) demonstrated a significant odds reduction (30%; SE, 4%) in patients allocated antiplatelet (mainly aspirin\textsuperscript{91,122–126}; Table 9) compared to control in suspected acute MI (10.4% vs 14.2%) translating into a benefit of 38 ± 5 (p < 0.0001) fewer serious vascular events (13 ± 2 fewer recurrent myocardial infarctions, p < 0.0001; 2 ± 1 fewer nonfatal strokes, p = 0.02; or 23 ± 4 fewer vascular deaths, p < 0.0001) per 1,000 patients treated for approximately 1 month. Total mortality was also significantly lower in the antiplatelet group compared to control group (9.2% vs 11.5%; 24 ± 4 fewer deaths per 1,000 patients treated, p < 0.0001) [Table 10]. The benefit was substantially larger than the excess risk of major extracranial bleeding (estimated to be one to two bleeds per 1,000 patients allocated antiplatelet therapy).\textsuperscript{121} With the exception of clopidogrel (see following), direct comparisons of aspirin with either other oral antiplatelet agents\textsuperscript{127–129} or aspirin plus another oral antiplatelet agent\textsuperscript{130} have not supported an advantage of other agents over, or in addition to, aspirin. Dosing of aspirin has not been well addressed in acute MI studies\textsuperscript{131}; as noted above, the largest trial (ISIS-2\textsuperscript{91}) demonstrating a reduction in vascular mortality with aspirin utilized 162.5 mg acutely and then daily for 1 month.

2.1 Aspirin

Recommendations

2.2.1. For patients with acute STE MI whether or not they receive fibrinolytic therapy, we recommend aspirin (160 to 325 mg po) over no aspirin therapy at initial evaluation by healthcare personnel (Grade 1A) followed by indefinite therapy (75 mg to 162 mg/d po) [Grade 1A].

Clopidogrel

Two recent trials\textsuperscript{132,133} of clopidogrel added to aspirin and other standard therapy in acute STE MI demonstrated important benefits of dual oral antiplatelet treatment (Tables 11, 12). Clopidogrel as Adjunctive Reperfusion Therapy/Thrombolysis in Myocardial Infarction\textsuperscript{132} enrolled patients (n = 3,491) 18 to 75 years old with STE MI within 12 h of symptom onset. Patients received aspirin, fibrinolysis and, for those receiving a fibrin-specific lytic, heparin. Patients were randomized to receive either clopidogrel (300-mg loading dose, then 75 mg qd) or placebo in a double-blind fashion up to and including the day of coronary angiography (48 to 192 h). Treatment with clopidogrel resulted in a high statistically significant 36% reduction (21.7 to 15.0%, p < 0.001) in the odds of an occluded IRA on the angiogram (performed in 94% of patients a median of 84 h after randomization), or death or recurrent MI by the start of coronary angiography, the latter two of which served as surrogates for failed reperfusion or reocclusion of the IRA. By 30 days, treatment with clopidogrel reduced the odds of cardiovascular death, recurrent MI, or recurrent ischemia leading to urgent revascularization by 20% (14.1 to 11.6%, p = 0.03). In terms of the individual clinical cardiovascular end points, there was no difference in cardiovascular mortality (clopidogrel, 2.6%; vs placebo, 2.2%; p = 0.49), a trend toward fewer recurrent MIs (2.5% vs 3.6%, p = 0.08), a 24% odds reduction in recurrent myocardial ischemia leading to urgent revascularization (p = 0.11), and a 46% odds reduction in stroke (p = 0.052). An ECG substudy\textsuperscript{134} found no difference in the rate of complete STE resolution between the clopidogrel and placebo groups at 90 min (38.4% vs 36.6%). However, clopidogrel was associated with a reduction in the odds of an in-hospital death or myocardial reinfarction in patients who achieved partial STE resolution (0.30, p = 0.003) or complete STE resolution (0.49, p = 0.056) at 90 min, suggesting that improvement in late IRA patency and clinical outcomes with clopidogrel is likely derived by preventing reocclusion of open arteries rather than by facilitating early reperfusion. The incidence of TIMI major bleeding was low and similar in both treatment arms (1.3% in the clopidogrel group vs 1.1% in the placebo group, p = 0.64). Similarly, there was no difference in the rates of ICH (0.5% in the clopidogrel group vs 0.7% in the placebo group, p = 0.38). Of note, 136 patients underwent coronary artery bypass graft surgery during their index hospitalization. Among these patients, treatment with clopidogrel was not associated with a significant excess of major bleeding through 30 days (7.5% with clopidogrel vs 7.2% with placebo, p = 1.00), even in those who underwent coronary artery bypass graft surgery within 5 days of discontinuation of study medication (9.1% vs 7.9%, respectively; p = 1.00).\textsuperscript{135}

The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study\textsuperscript{2} also evaluated the role of clopidogrel in addition to 162 mg/d of aspirin in the management of patients (n = 45,852) with suspected MI.\textsuperscript{133} Patients pre-
Table 9—Randomized Trials of Aspirin Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.1)*

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features (%)</th>
<th>Time From Symptom Onset to Randomization h</th>
<th>Aspirin Regimen</th>
<th>Control</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No/Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-Pilot125 1987</td>
<td>Suspected MI, symptom onset ≤ 24 h</td>
<td>Aspirin 6.7 h, Placebo 6.4 h†</td>
<td>Enteric-coated 325 mg on alternate days for 28 d</td>
<td>Placebo</td>
<td>30</td>
<td>Aspirin: 25/313 (8.0) Placebo: 35/306 (11.4)</td>
<td>Fibrinolysis administered to patients ≤ 70 yr who had symptoms &lt; 4</td>
</tr>
<tr>
<td>ISIS-2128 1988</td>
<td>Suspected MI, symptom onset ≤ 24 h, STE &gt; 2 mm in precordial leads and absence of Q waves</td>
<td>Aspirin 244 ± 42 min, Placebo 248 ± 48 min</td>
<td>Placebo</td>
<td>Placebo</td>
<td>3 mo</td>
<td>Aspirin: 10/50 (20) Placebo: 12/50 (24) h</td>
<td>Patient died of pneumonia; no cardiac deaths</td>
</tr>
<tr>
<td>Verheught et al 1990</td>
<td>First anterior MI (STE &gt; 2 mm in precordial leads and absence of Q waves)</td>
<td>Aspirin 244 ± 42 min, Placebo 248 ± 48 min</td>
<td>Placebo</td>
<td>Placebo</td>
<td>3 mo</td>
<td>Aspirin: 10/50 (20) Placebo: 12/50 (24) h</td>
<td>Fibrinolysis administered to patients ≤ 70 yr who had symptoms &lt; 4</td>
</tr>
<tr>
<td>Rasmanis et al 1998</td>
<td>Acute MI, symptom onset ≤ 24 h</td>
<td>Mean 9.3 h</td>
<td>500 mg in buffered water solution 12 h post-admission and every third day thereafter</td>
<td>Placebo</td>
<td>30</td>
<td>Aspirin: 0/10 (0) Placebo: 1/101 (10)</td>
<td></td>
</tr>
<tr>
<td>Johannessen et al 1989</td>
<td></td>
<td>150 mg</td>
<td></td>
<td></td>
<td>14</td>
<td>Aspirin: 0/11 (0) Placebo: 0/9 (0)</td>
<td></td>
</tr>
<tr>
<td>Boehringer Ingelheim (unpublished) 1976</td>
<td>Information not available</td>
<td>Information not available</td>
<td>1,320 mg</td>
<td>Information not available</td>
<td>14</td>
<td>Aspirin: 1/25 (4.0) Placebo: 1/25 (4.0)</td>
<td>Internal report: Asasantin DVT nach Myokardinfarkt: Bracknell, Berkshire; Boehringer Ingelheim§</td>
</tr>
<tr>
<td>Meijer et al (APRICOT) 1993</td>
<td>Age &lt; 70 yr, STE &lt; 4 h treated with fibrinolysis with patient IRA</td>
<td>Aspirin = 27, Placebo = 24</td>
<td>325 mg/d</td>
<td>Placebo</td>
<td>3 mo</td>
<td>Aspirin: 1/107 (0.9) Placebo: 2/95 (2.1)</td>
<td>Approximate mean time from symptom onset to angiography, after which patients were randomized</td>
</tr>
</tbody>
</table>

*Adapted from Antithrombotic Trialists' Collaboration.121
†Mean values.
‡Mean ± SD.
§Ingelheim, Germany.
sent within 24 h of symptom onset and had STE (87%), BBB (6%), or ST-segment depression (7%). While approximately 50% received fibrinolysis and 75% received an anticoagulant (mainly heparin), <5% of patients underwent PCI during the index hospitalization; thus, post-MI management differed substantially when compared to contemporary US-based practice. Treatment with clopidogrel resulted in a 9% RRR (95% CI, 3 to 14%; p = 0.002) in the incidence of death, reinfarction, or stroke through index hospitalization, corresponding to 9 ± 3 fewer events per 1,000 patients treated for approximately 2 weeks (mean, 14.9 days; quartiles, 9, 14, and 21 days). Despite a loading dose not having been used, the benefit of clopidogrel was evident within the first 12 h with an 11% RRR (99% CI, 0 to 20%; p = 0.014), mainly due to an 11% (99% CI, −1 to 22%; p = 0.019) proportional reduction in death (3.2% vs 3.6%). Indeed, the coprimary end point of death was significantly reduced with clopidogrel (7.5% vs 8.1%; RRR, 7%; 95% CI, 1 to 13%; p = 0.03). In terms of the other individual components of the composite end point, treatment with clopidogrel resulted in a significant (2.1% vs 2.4%; OR, 0.86; 95% CI, 0.76 to 0.9; p = 0.02) in reinfarction and a nonsignificant (0.9% vs 1.1%; OR, 0.86; 95% CI, 0.72 to 1.03; p = 0.11) reduction in stroke. Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel, either overall (0.58% vs 0.55%, p = 0.59), or in patients >70 years old (26% of the overall study population), or in those given fibrinolytic therapy.

While the duration of clopidogrel therapy after STE MI has been limited to 28 days (in patients not receiving a coronary stent),133 data from the CURE trial136 in non-STE ACS suggest not only an early benefit, but an ongoing and potentially incremental reduction in cardiovascular death, repeat MI, or stroke with clopidogrel compared to placebo (5.2% vs 6.3%; RR, 0.82; 95% CI, 0.70 to 0.95 in patients who had not had an event by 30 days, from day 31 to 365).137 There was a small excess of major bleeding over this mean of 8 months (1.75% vs 1.18%; RR, 1.48; 95% CI, 1.1 to 1.99; absolute excess, 0.57%); however, life-threatening bleeding rates were similar (0.91% vs 0.83%; RR, 1.09; 95% CI, 0.75 to 1.59; absolute excess, 0.08%) and could potentially be further offset by using a lower dose of aspirin (<100 mg/d).138 It is plausible that the net benefit of clopidogrel at 75 mg/d in addition to aspirin beyond 30 days and up to 1 year in non-STE ACS patients (which included approximately 3,300 patients with MI), could be extended to patients presenting with STE MI.

Although clopidogrel is used routinely as adjunctive therapy for coronary stenting, there are no randomized trials of clopidogrel before coronary angiography in patients with STE MI undergoing primary PCI. Further, there are no comparisons of clopidogrel dosing regimens in STE MI (see chapter by Becker et al in this supplement). Neither the optimal nor minimal times from clopidogrel ingestion to performance of PCI have been clearly established.139,140 One approach could include loading with 300 mg or even >300 mg in order to achieve higher levels of antiplatelet activity more rapidly and in view of the potential (but not definitively proven, especially in STE MI) clinical benefit of higher clopidogrel dosing.141,142 For patients undergoing primary PCI and receiving a glycoprotein (GP) IIb/IIIa inhibitor (see following), it is unclear whether clopidogrel provides incremental efficacy. However, given the very small chance that a patient would require emergent coronary artery bypass surgery coupled with the apparent benefit of clopidogrel administered 2 to 8 days prior to (nonprimary) PCI in patients with recent STE MI,143 clopidogrel could be administered immediately after the diagnosis of STE MI has been made and need not await visualization of the coronary anatomy in a patient about to undergo primary PCI. After the loading dose, 75 mg/d should be considered (for duration of therapy, see chapter by Becker et al in this supplement).

2.2 Clopidogrel

Recommendations

2.2.1. For patients with acute STE MI, we recommend clopidogrel in addition to aspirin (Grade 1A). The recommended dosing for clopi-
dogrel is 300 mg po for patients ≤ 75 years old and 75 mg po for patients > 75 years old if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/d po for up to 28 days (Grade 1A).

2.2.2. For patients with acute STE MI who have not received a coronary stent, we suggest that clopidogrel, 75 mg/d, could be continued beyond 28 days and up to 1 year (Grade 2B).

2.2.3. For patients undergoing primary PCI, we suggest clopidogrel in addition to aspirin with a recommended initial dosing of at least 300 mg (Grade 1B), followed by 75 mg/d (for duration of therapy, see chapter by Becker et al in this supplement).

2.3 Antithrombin Therapy

Recommendation

2.3.1. For patients with acute STE MI, in addition to aspirin and other antiplatelet therapies, we recommend the use of antithrombin therapy over no antithrombin therapy (Grade 1A), including for those patients receiving fibrinolysis (and regardless of which lytic agent is administered), primary PCI, or patients not receiving reperfusion therapy.

2.4 UFH

Continued controversy exists regarding the role of UFH in STE MI. Based on 21 small randomized trials in which no routine aspirin was used among patients (n = 5459) with suspected acute MI, a systematic overview demonstrated a significant reduction in mortality (11.4% vs 14.9%; RRR, 25%; 95% CI, 10 to 38%; p = 0.002) with heparin (Table 13). In addition to the 35 (SE ± 11) fewer deaths per 1,000 patients treated, there were also 10 ± 4 fewer strokes (p = 0.01), 15 ± 8 fewer pulmonary emboli (p < 0.001), and nonsignificantly 15 ± 8 fewer reinfarctions (p = 0.08) per 1,000 patients treated. Heparin compared with no heparin did result in 10 ± 4 more major bleeds (p = 0.01). However, given that no routine aspirin was administered in these trials (and most patients did not receive fibrinolytic therapy), the overview also examined the role of heparin in the presence of aspirin. Approximately 68,000 patients have been randomly assigned in seven trials to either aspirin plus heparin or aspirin alone; 93% of these patients also received fibrinolytic therapy (Tables 13, 14). The benefit of heparin was more modest, with 5 ± 2 fewer deaths (p = 0.03), 3 ± 1 fewer reinfarctions (p = 0.04), and 1 ± 0.4 fewer pulmonary emboli.
heparin use led to 1.1 more strokes, and 3.1 more major bleeds (p < 0.001) per 1,000 patients treated.

Most of this evidence about adding heparin to aspirin therapy comes from the patients (n = 62,067) who received fibrinolytic therapy in the GISSI-2148 and ISIS-3 32 trials (Table 12). In both studies, heparin therapy was begun several hours (12 h in GISSI-2 and 4 h in ISIS-3) after the start of any fibrinolytic therapy, and the heparin was given subcutaneously (12,500 IU bid for about 1 week), which caused further delay.149 During the period of scheduled heparin treatment in these two trials, there was some evidence of a reduction in mortality (6.8% with heparin, aspirin, and fibrinolytic therapy, compared with 7.3% with aspirin and fibrinolytic therapy alone), suggesting the prevention of about 5 deaths per 1,000 patients treated. However, there was no significant difference in the observed effects of heparin between patients receiving tPA and those receiving streptokinase or anistreplase, or between patients who did and did not receive aspirin.

In the GUSTO-I trial,37 among patients receiving streptokinase (n = 20,251) the SC heparin regimen utilized in the ISIS-3 trial32 was compared with at least 48 h of IV heparin (bolus of 5,000 IU followed by an infusion of 1,000 IU/h, adjusted to a target APTT of 60 to 85 s151). IV UFH was not associated with any reduction in mortality or stroke, and there was a significant excess of reinfarctions (7.3 more per 1,000 patients, p < 0.01). Of note, however, is that there was a 36% crossover rate from SC to IV UFH in this trial.

In a series of angiographic trials (Table 13),145,152,153 IV UFH led to higher rates of IRA patency in conjunction with alteplase; a direct relation between duration of APTT and the likelihood of IRA perfusion was also observed.145,153 However, the effects of IV UFH on clinical outcomes remains unconvincing.150 Further, when more intensive IV UFH regimens were initially studied in three trials154–156 of patients receiving fibrinolytic therapy, excessive rates of ICH and other major bleeding prompted the premature termination of these trials and modification of the IV UFH dose subsequently. While earlier large trials37,38,82,83 with

(p = 0.01); heparin use led to 1 ± 1 more strokes, and 3 ± 1 more major bleeds (p < 0.001) per 1,000 patients treated.

Table 12—Clopidogrel Therapy for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.2)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Clopidogrel</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1771/24,713 (7.2)</td>
<td>1,883/24,630 (7.6)</td>
<td>0.93 (0.87–1.00)</td>
<td>5 (2)</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 13—UFH Therapy for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.3)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>UFH</th>
<th>Control</th>
<th>Odds Reduction, % (SE) or OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials with no routine aspirin, No.*†</td>
<td>284/2,684 (11.4)</td>
<td>378/2,775 (14.9)</td>
<td>25 (8)</td>
<td>35 (11)</td>
<td>High</td>
</tr>
<tr>
<td>Trials with routine aspirin*‡</td>
<td>2,932/34,035 (8.6)</td>
<td>3,092/34,055 (9.1)</td>
<td>6 (3)</td>
<td>5 (2)</td>
<td>High</td>
</tr>
<tr>
<td>Trials with IV UFH and routine fibrinolytic therapy§</td>
<td>45/878 (5.1)</td>
<td>48/857 (5.6)</td>
<td>0.91 (0.59–1.39)</td>
<td>5 (11)</td>
<td>High</td>
</tr>
</tbody>
</table>

*Includes all randomized trials meeting inclusion criteria for the quantitative review by Collins et al.144
†Follow-up in-hospital to 28 days; 14% of patients in these trials were given fibrinolytic therapy.
‡Follow-up in-hospital to 14 days; 93% of patients in these trials were given fibrinolytic therapy.
§Includes all randomized trials meeting inclusion criteria for the quantitative review by Mahaffey et al150; follow-up in hospital.
Table 14—Selected Randomized Trials of UFH Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.3)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Heparin Regimen, Dose, Duration, APTT Adjustment</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Fibrinolytic(s)</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-Pilot 125 1987</td>
<td>Suspected MI, symptom onset ≤ 24 h, no specific ECG criteria</td>
<td>IV 1,000 U/h for 48 h, starting 12 h after the end of streptokinase infusion, no APTT adjustment</td>
<td>No</td>
<td>Enteric-coated 325 mg on alternate days for 28 d (50%)</td>
<td>Streptokinase (2/3)</td>
<td>In-hospital (median 9)</td>
<td>Heparin: 25/314 (8.0) Control: 26/305 (8.5)</td>
<td>Primary endpoint was death plus late (&gt; day 4) clinical congestive heart failure or extensive left ventricular damage (left ventricular ejection fraction ≤ 35% or ≥ 45% myocardial segments injured by echocardiography or follow-up ECG QRS score &gt; 10): 1,403/6,175 (22.7%) vs 1,419/6,206 (22.9%), RR 0.99 (95% CI 0.91–1.08) Includes 12,490 patients in the GISSI-2 trial 150 and 8,401 patients recruited in 13 other countries (366/4186 [8.7%] vs 358/4201 [8.5%]); in 525/4,186 patients randomized to receive SC UFH, UFH not started or interrupted or given in lower dosage</td>
</tr>
<tr>
<td>GISSI-2 1990</td>
<td>Symptom onset ≤ 6 h, STE 100</td>
<td>SC 12,500 U bid, starting 12 h after initiation of fibrinolytic, continued until hospital discharge, no APTT adjustment</td>
<td>No</td>
<td>300–325 mg/d</td>
<td>Streptokinase (50%), tPA over 3 h (50%)</td>
<td>35</td>
<td>Heparin: 518/6175 (8.3) Control: 574/6,206 (9.3)</td>
<td></td>
</tr>
<tr>
<td>ISG 36 1990</td>
<td>Symptom onset ≤ 6 h, STE 100</td>
<td>SC 12,500 U bid, starting 12 h after initiation of fibrinolytic, continued until hospital discharge, no APTT adjustment</td>
<td>No</td>
<td>300–325 mg/d</td>
<td>Streptokinase (50%), tPA over 3 h (50%)</td>
<td>35</td>
<td>Heparin: 884/10361 (8.5) Control: 932/10407 (8.9) RR 0.95 (0.86–1.04)</td>
<td></td>
</tr>
<tr>
<td>Bleich et al 152 1990</td>
<td>Symptom onset ≤ 6 h; STE 100</td>
<td>IV 5,000 U bolus followed by 1,000 U/h until catheter (48–72 h), adjusted to target APTT 1.5-2 times control</td>
<td>No</td>
<td>None</td>
<td>tPA over 3 h</td>
<td>In-hospital</td>
<td>Heparin: 6/46 (13.0) Control: 5/49 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Hsia et al (HART) 153 1990</td>
<td>Age ≤ 75 yr; symptom onset ≤ 6 h; STE 100</td>
<td>IV 5,000 U bolus followed by 1,000 U/h at initiation of lysis, for 7 d, adjusted to target APTT 1.5-2 times baseline</td>
<td>No</td>
<td>80 mg/d in patients not receiving heparin</td>
<td>tPA over 4 h</td>
<td>7</td>
<td>Heparin: 2/106 (1.9) Control (aspirin): 4/99 (4.0)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 14—Continued

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Heparin Regimen, Dose, Duration, APTT Adjustment</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Fibrinolytic(s)</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-3&lt;sup&gt;265&lt;/sup&gt; 1992</td>
<td>Suspected MI; symptom onset ≤ 24 h; STE 77; BBB 4; ST-segment depression 7 Other 8 Normal 3</td>
<td>SC 12,500 U starting 4 h after randomization and then bid for 7 d or until discharge; no APTT adjustment</td>
<td>No</td>
<td>162 mg/d</td>
<td>Streptokinase &lt;br&gt;(1/3), tPA over 4 h (1/3), APSAC (1/3)</td>
<td>35</td>
<td>Heparin: 2,132/20,656 (10.3)&lt;br&gt;Control: 2,189/20,643 (10.6)</td>
<td>10% of patients randomized to SC UFH received IV UFH and 18% of patients randomized to receive no heparin received IV or high-dose SC UFH</td>
</tr>
<tr>
<td>Col et al (OSIRIS)&lt;sup&gt;146&lt;/sup&gt; 1992</td>
<td>Age ≥ 70 yr; symptom onset ≤ 6 h; STE 100</td>
<td>IV 5,000 U bolus followed by 1,000 U/h until catheter at 48–120 h, no APTT adjustment</td>
<td>Yes</td>
<td>250 mg IV bolus or 300 mg po, then 75–125 mg po on alternate days</td>
<td>tPA over 3 h</td>
<td>In-hospital</td>
<td>Heparin: 9/324 (2.8)&lt;br&gt;Placebo: 11/320 (3.4)</td>
<td>652 patients randomized; data available for 644</td>
</tr>
<tr>
<td>O’Connor et al (DUCCS)&lt;sup&gt;1&lt;/sup&gt; 1994</td>
<td>Symptom onset ≤ 6 h; STE 100</td>
<td>IV 10,000 U bolus before lysis followed by 1,000 U/h for 24 h; APTT adjustment unknown</td>
<td>Yes</td>
<td>200 mg/d</td>
<td>Streptokinase</td>
<td>In-hospital</td>
<td>Heparin: 1/64 (1.6)&lt;br&gt;Placebo: 3/64 (4.7)</td>
<td>—</td>
</tr>
<tr>
<td>O’Connor et al (DUCCS)&lt;sup&gt;1&lt;/sup&gt; 1994</td>
<td>Age ≤ 85 yr; symptom onset ≤ 12 h; STE 100</td>
<td>IV 15 U/kg/h 4 h after lysis for 5 d; adjusted to target APTT 50–90 s</td>
<td>No</td>
<td>325 mg/d</td>
<td>APSAC</td>
<td>14</td>
<td>Heparin: 12/128 (9.4)&lt;br&gt;Control: 8/122 (6.6)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Adapted from Collins et al.<sup>144</sup> Collins et al.<sup>145</sup> and Malik et al.<sup>150</sup>
alteplase generally utilized a 5,000-IU bolus followed by an initial infusion of 1,000 IU/h of IV UFH, observational data support a weight-adjusted bolus with a lower APTT with a target APTT of 50 to 70 s (approximately 1.5 to 2 times the control value). For fibrin-specific (alteplase, reteplase, and tenecteplase), fibrinolytic-treated patients, a 60 U/kg bolus (maximum, 4,000 U for patients weighing >70 kg) followed by a maintenance infusion of 12 U/kg/h (maximum, 1000 U/h) initial infusion is suggested. In the ASSENT-3 trial, this suggested that discontinuation of UFH after 24 h after alteplase (where patients received an UFH bolus of 60 U/kg bolus and a 5,000-U bolus and 1,000 U/h infusion for patients >67 kg; target APTT, 50 to 75 s). An APTT measurement and dose adjustment was made at 3 h, and subsequent remeasurement obtained 6 h after each dose adjustment until the target range was achieved, and daily thereafter.

The above mentioned clinical trials involving IV UFH have used universal therapeutic APTT ranges, typically 50 to 70 s, regardless of the responsiveness of the thromboplastin reagent in use at the participating institutions. There is wide variability in APTT measurement between laboratories, and it is not known what UFH level, as measured by anti-Xa activity, corresponds with an APTT of 50 to 70 s. For most thromboplastin reagents, this corresponds to 0.2 to 0.5 U/mL heparin by anti-Xa activity. Consensus conferences of The College of American Pathologists and the American College of Chest Physicians and other sources have recommended against these generalization of therapeutic APTT ranges. There is wide agreement that therapeutic APTT ranges should be customized for the specific thromboplastin reagent in use; however, since clinical trials have failed to do so, evidence-based recommendations for use of UFH for cardiac indications are difficult to make. Our recommendations are based on the APTT ranges as they are described in published studies; however, institutions that have established therapeutic APTT ranges (eg, 1.5 to 2 times control) in the recommended fashion are encouraged to continue using them. The implementation of a discrepant universal therapeutic range at such an institution may lead to systematic errors in heparin dosing (see chapter by Hirsh et al in this supplement).

The ideal duration of UFH in STE MI remains uncertain. The only randomized trial to address this issue suggested that discontinuation of UFH after 24 h after alteplase (where patients received aspirin and dipyridamole compared with maintaining UFH for 7 to 10 days after MI) did not lead to any difference in late coronary artery IRA patency. There was a trend toward more clinical events (death, reinfarction, or stroke) in the continued IV UFH group (10.1% vs 4.8%, p = 0.091) and no differences seen in bleeding complications; however, this study lacked power (n = 202) to detect potentially modest but clinically important differences. Thus, the most common approach has been to use IV UFH for approximately 48 h after which time it is discontinued in low-risk patients, given subcutaneously in patients at high risk of systemic embolization, and given IV in patients at high risk for coronary reocclusion. Despite concerns about heparin “rebound” after UFH discontinuation, no specific UFH strategy has been tested to attempt to reduce this apparent increased risk for recurrent thrombosis; however, some studies of other antithrombotic agents (eg, enoxaparin, fondaparinux; see following) have employed longer treatment durations.

There are no randomized trials evaluating the use of UFH compared with no antithrombin therapy in primary PCI. Some studies (but not in STE MI) have retrospectively related activated clotting time (ACT) values to ischemic and bleeding outcomes, leading to a previous recommendation that IV UFH be administered in a weight-adjusted dose of 60 to 100 U/kg with a target ACT from 250 to 350 s in the absence of GP IIb/IIIa inhibitors and 50 to 70 U/kg with a target ACT > 200 s when administered with adjunctive GP IIb/IIIa inhibition. However, in the setting of frequent clopidogrel, GP IIb/IIIa inhibitor, and stent use, and including patients requiring urgent (but not primary) PCI, an analysis of several trials (n = 8,369) suggested that ACT does not correlate with ischemic complications and had a modest association with bleeding complications, driven mainly by minor bleeding. Thus, the option of not performing routine ACT monitoring could also be considered, particularly in those patients receiving a GP IIb/IIIa inhibitor with IV UFH.

The role of IV UFH to potentially achieve IRA patency (ie, UFH as reperfusion therapy) was explored in a pilot study in STE MI patients subsequently undergoing coronary angiography and primary PCI. Based on promising IRA patency (TIMI flow grade 2 or 3) results using 300 IU/kg IV UFH compared to a matched control, a randomized comparison of high-dose to no/low-dose UFH (0 IU or 5,000 IU if treated in a PCI or non-PCI center followed by transfer, respectively) was made in STE MI patients (n = 584) prior to undergoing primary PCI within 6 h of symptom onset. All patients received aspirin (500 mg IV or 300 mg po) and IV nitroglycerin, and an IV infusion of UFH (target
APTT, 2 to 3 times normal) after PCI for 24 to 48 h. However, in contrast to the pilot study results, IRA patency (22% vs 21%, p > 0.1), including TIMI flow grade 3 (15% vs 9%, p = 0.11) was similar in the two treatment groups. There were also no differences in the clinical end points between the two groups. There were no hemorrhagic strokes; however, there was a nonsignificant trend toward greater need for blood transfusion in the high-dose IV UFH group (10% vs 6%, p = 0.07). No subsets of patients showed beneficial effects of high-dose UFH, such as patients with longer delay between heparin administration and coronary angiography or patients with short delay between symptom onset and admission. Thus, there was no benefit of high-dose IV bolus UFH on early patency or clinical outcomes compared with no or low-dose heparin in patients prior to undergoing primary angioplasty.

2.4 UFH

Recommendations

2.4.1. For patients receiving streptokinase, we suggest administration of either IV UFH (5,000-U bolus followed by 1,000 U/h for patients > 80 kg, 800 U/h for < 80 kg) with a target APTT of 50 to 75 s or SC UFH (12,500 U q12h) over no UFH therapy for 48 h (both Grade 1B).

2.4.2. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis in acute MI, we recommend administration of weight-adjusted heparin (60 U/kg bolus for a maximum of 4,000 U followed by 12 U/kg/h [1,000 U/h maximum]) adjusted to maintain an APTT 50 to 70 s for 48 h (Grade 1B).

2.4.3. For patients with STE MI undergoing primary PCI, we recommend administration of IV UFH over no UFH therapy (Grade 1C). The recommended periprocedural dosing in patients receiving a GP IIb/IIIa inhibitor is 50 to 70 U/kg (target ACT > 200 s); in patients not receiving a GP IIb/IIIa inhibitor, the recommended periprocedural dosing is 60 to 100 U/kg (target ACT, 250 to 350 s).

Low-Molecular-Weight Heparin

The low-molecular-weight heparins (LMWHs) have a number of attractive pharmacologic properties compared with UFH177,178 (see chapter by Hirsh et al in this supplement). Several small randomized studies have examined rates of IRA patency179–181 and reocclusion,180,182,183 left ventricular thrombus formation/arterial thromboembolism,184 and clinical outcomes181–183,185,186 with LMWH178 as compared to placebo179,182,184,185 (Tables 15, 16) or UFH180,181,183,186 (Tables 17, 18). More recently, moderate-to-large randomized clinical outcome trials comparing LMWH to placebo187 (Tables 15, 16) and to UFH184,186,188 (Tables 17, 18) in the setting of fibrinolysis have been completed.

Combined, four small studies179,182,184,185 (n = 1,376) comparing LMWH to placebo (as adjunctive therapy to fibrinolysis in two studies179,182 and starting LMWH 5 to 8 days after lysis in two studies184,185) suggested no difference in mortality (6.4% vs 6.8%; OR, 0.75; 95% CI, 0.36 to 1.55), a reduction in reinfarction (3.2% vs 6.0%; OR, 0.54; 95% CI, 0.33 to 0.91), an increase in major bleeding (3.6% vs 1.0%; OR, 3.00; 95% CI, 1.50 to 6.00), and a numerically higher rate of ICH (0.44% vs 0.15%; OR, 2.01; 95% CI, 0.40 to 9.99).189

The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation187 was a randomized, double-blind, placebo-controlled trial of patients (n = 15,570) with STE or new left BBB presenting within 12 h of symptom onset. Reviparin (3,436 IU for < 50 kg, 5,153 IU for 50 to 75 kg, or 6,871 IU for > 75 kg q12h SC was compared to placebo for 7 days (76% of patients), with 91% receiving treatment for at least 2 days. Aspirin was used in 97% of patients and clopidogrel or ticlopidine in 55% during the hospitalization; fibrinolytic therapy was used in 73% of patients and primary PCI in 6%. In patients undergoing primary PCI, open-label UFH was used during the procedure, with study medication being initiated 1 h after removal of the sheath. The 7-day composite end point of death, MI, or stroke was reduced in the reviparin group (9.6% vs 11.0%; hazard ratio [HR], 0.87; 95% CI, 0.79 to 0.96; p = 0.005). The second coprimary outcome, which included recurrent ischemia with ECG changes, was also significantly reduced with reviparin (11.1% vs 12.6%; HR, 0.87; 95% CI, 0.80 to 0.96; p = 0.004). There were also significant reductions in mortality (8.0% vs 8.9%; HR, 0.89; 95% CI, 0.80 to 0.99; p = 0.04) and reinfarction (1.6% vs 2.1%; HR, 0.75; 95% CI, 0.60 to 0.95; p = 0.02). There was no significant difference in strokes (0.8% vs 0.6%; HR, 1.24; 95% CI, 0.55 to 1.81; p = 0.26) but a small, significant excess of hemorrhagic strokes (0.3% vs 0.1%, p = 0.03). At 30 days, both composite outcomes were similarly reduced, including death, reinfarction, or disabling stroke (11.6% vs 13.3%; HR, 0.87; 95% CI, 0.79 to 0.95; p = 0.002); death (9.8% vs 11.3%; HR, 0.87; 95% CI, 0.79 to 0.96; p = 0.005) and reinfarction (2.0% vs 2.6%; HR, 0.77; 95% CI, 0.62 to 0.95; p = 0.01) were also significantly lower with reviparin compared to placebo.

The benefits of reviparin were greatest with earlier
Table 15—Randomized Trials of LMWH Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.4)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Heparin Regimen, Dose, Duration</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Reperfusion Therapy</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontny et al (FRAMI) 1997</td>
<td>Suspected evolving anterior Q wave MI (Q waves or STE), symptom onset ≤ 6 h</td>
<td>Dalteparin 150 U/kg (maximum 100 kg) SC, started 8 h after lysis, then q12h, continued until hospital discharge</td>
<td>Yes</td>
<td>300 mg initially, 160 mg/d</td>
<td>Streptokinase</td>
<td>9 ± 2</td>
<td>Dalteparin: 21/388 (5.4) Placebo: 23/388 (5.9)</td>
<td>Warfarin instead of aspirin in patients considered at high risk of thromboembolic events (eg, thrombus, severe wall motion abnormalities)</td>
</tr>
<tr>
<td>Frostfeldt et al (Biomacs II) 1999</td>
<td>Symptom onset ≤ 12 h, STE or left BBB</td>
<td>Dalteparin 100 U/kg (maximum 100 kg) SC, started before lysis, then 120 U/kg 12 h later (maximum 1,000 U)</td>
<td>Yes</td>
<td>300 mg initially, 75 mg/d thereafter</td>
<td>Streptokinase</td>
<td>21</td>
<td>Dalteparin: 4/54 (7.4) Placebo: 6/47 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Simoons et al (AMI-SK) 2002</td>
<td>Symptom onset ≤ 12 h, STE 100</td>
<td>Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for 3–8 d</td>
<td>Yes</td>
<td>100–325 mg/d</td>
<td>Streptokinase</td>
<td>30</td>
<td>Enoxaparin: 17/253 (6.7) Placebo: 17/243 (7.0)</td>
<td></td>
</tr>
<tr>
<td>CREATE 2005</td>
<td>Symptom onset ≤ 12 h, STE or new left BBB</td>
<td>Reviparin 3,436 U for patients &lt; 50 kg, 5,133 U for patients 50–75 kg, and 6,871 U for patients &gt; 75 kg SC q12h</td>
<td>Yes</td>
<td>97% of patients, dose unknown</td>
<td>Fibrinolysis (74%), primary PCI (9%)</td>
<td>30</td>
<td>Reviparin: 766/7,780 (9.8) Placebo: 877/7,790 (11.3) HR 0.87 (95% CI 0.79–0.96)</td>
<td>Open-label UFH used in patients undergoing primary PCI with study medication initiated 1 h after sheath removal</td>
</tr>
</tbody>
</table>
treatment after symptom onset at 7 days (<2 h: HR, 0.70; 95% CI, 0.52 to 0.96; p = 0.03; 30 events prevented per 1,000 patients; 2 to < 4 h: HR, 0.81; 95% CI, 0.67 to 0.98; p = 0.03; 21 events prevented per 1,000 patients; 4 to < 8 h: HR, 0.85; 95% CI, 0.73 to 0.99; p = 0.05; 16 events prevented per 1,000 patients; and ≥ 8 h: HR, 1.06; 95% CI, 0.86 to 1.30; p = 0.58; p = 0.04 for trend). Similar results were evident at 30 days (p = 0.01 for trend), and similar trends were observed for mortality and MI but not for strokes. Consistent benefits at 7 days were observed in those patients undergoing reperfusion therapy (HR, 0.90; 95% CI, 0.81 to 1.01) and in those not receiving this therapy (HR, 0.79; 95% CI, 0.65 to 0.95; p = 0.23 for interaction) for death, MI, or stroke. Similar results were observed for the second coprimary outcome (death, MI, stroke, or recurrent ischemia with ECG changes). In the subgroup of patients (n = 949) undergoing primary PCI, trends toward fewer events were also observed (5.8% vs 7.3%; HR, 0.79; 95% CI, 0.48 to 1.31; for the first coprimary outcome; and 7.3% vs 10.0%; HR, 0.71; 95% CI, 0.46 to 1.10; for the second coprimary outcome). In the subgroup of patients (n = 1,052) who received alteplase or primary PCI, the rates of death, reinfarction, stroke, or recurrent ischemia with ECG changes were consistent with the overall findings (5.8% vs 7.7%; HR, 0.75; 95% CI, 0.47 to 1.19), suggesting that the benefits of reviparin were independent of the type of reperfusion therapy.

There was a significant increase in the rates of life-threatening or major bleeding at 7 days with reviparin (0.9% vs 0.4%; HR, 2.49; 95% CI, 1.61 to 3.87; p < 0.001), and the increased bleeding risk tended to be greater in those patients undergoing reperfusion therapy (1.1% vs 0.4%); the rates were low in patients (n = 3,323) without reperfusion therapy (0.1% vs 0.1%, respectively). The net clinical benefit (composite outcome of 7-day death, myocardial reinfarction, strokes, and life-threatening bleeding) remained in favor of reviparin (9.8% vs 11.1%; HR, 0.88; 95% CI, 0.80 to 0.97; p = 0.01), with similar results at 30 days (12.0% vs 13.7%; HR, 0.87; 95% CI, 0.80 to 0.95; p = 0.002), suggesting that for every 1,000 patients treated with reviparin, 17 fewer major adverse outcomes would be prevented.

Five small-to-moderate sized trials62,84,181,186,190 have compared enoxaparin to UFH as an adjunct to fibrinolysis (including one study62 as a prehospital adjunct to tenectaplaste) and one study191 in MI patients ineligible for fibrinolysis. Combined, these studies (n = 7,960) suggested no difference in mortality (5.8% vs 6.1%; OR, 0.97; 95% CI, 0.81 to 1.17), a reduction in reinfarction (3.2% vs 5.1%; OR, 0.61; 95% CI, 0.48 to 0.76), an increase in major bleeds (3.2% vs 2.3%; OR, 1.38; 95% CI, 1.05 to 1.81), and a numeric but nonsignificant increase in ICH (1.2% vs 0.99%; OR, 1.30; 95% CI, 0.84 to 2.03).189 This overview189 did not include the small ASSENT PLUS study183 (n = 439) comparing dalteparin to UFH as an adjunct to alteplase that showed an early reinfarction reduction (7 days: 0.9% vs 5.2%, p = 0.01) but an apparent rebound once dalteparin was stopped; 30-day death/MI rates were similar when compared with UFH (9.1% vs 10.6%; on-treatment major bleeds (3.6% vs 5.2%) and ICH (0.4% vs 1.9%) were not significantly different. Another small study (n = 186) of parpamin compared to UFH as an adjunct to fibrinolysis was also more recently published.192

In the open label ASSENT-3 trial,84 patients were randomly assigned to one of three regimens: full-dose tenectaplaste and enoxaparin for up to 7 days (n = 2,040), half-dose tenectaplaste with weight-adjusted low-dose UFH and a 12-h infusion of the GP IIb/IIIa inhibitor abciximab (n = 2017), or full-dose tenectaplaste with weight-adjusted UFH for 48 h (n = 2,035). The primary, exploratory end points were the composites of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia (efficacy end point), and the above end point plus in-hospital ICH or in-hospital major bleeding complications (efficacy-plus-safety end point). There were significantly fewer efficacy end points in the enoxaparin and abciximab groups than in the UFH group: 11.4% and 11.1% vs 15.4% (RR, 0.74; 95% CI, 0.63 to 0.87; p = 0.0002; and RR, 0.72; 95% CI, 0.61 to 0.84; p < 0.0001; respectively). The same was true for the efficacy-plus-safety end point: 13.7% and 14.2% vs 17.0% (RR, 0.81; 95% CI, 0.70 to 0.93; p = 0.0037; and RR, 0.84; 95% CI, 0.72 to 0.96; p = 0.014; respectively). There were no significant differences in 30-day mortality, in-hospital ICH, or major bleeding between the enoxaparin and UFH groups, and the 95% CIs around the point estimates were relatively wide given the moderate sample size of the ASSENT-3 trial. Further, the
### Table 17—Randomized Trials of LMWH vs UFH in Suspected Acute MI: Clinical Description and Results (Section 2.4)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>LMWH Regimen, Dose, Duration</th>
<th>UFH Regimen, Dose, Duration</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Fibrinolytic(s)</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ross et al (HART II) 2001</td>
<td>Symptom onset ( \leq 12 ) h STE 100</td>
<td>Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for ( \geq 3 ) d</td>
<td>IV bolus 4,000 U for weight ( &lt; 67 ) kg, 5,000 U for weight ( \geq 67 ) kg, followed by infusion 15 U/kg/h for ( \geq 3 ) d, adjusted to target APTT 2–2.5 times control</td>
<td>No</td>
<td>Yes, dose unknown</td>
<td>tPA</td>
<td>30</td>
<td>Enoxaparin: 9/196 (4.5) UFH: 10/197 (5.0)</td>
<td>Boluses administered before fibrinolysis; initial APTT sample drawn after 3 h</td>
</tr>
<tr>
<td>ASSENT-3 2001</td>
<td>Symptom onset ( \leq 6 ) h; STE or left BBB</td>
<td>Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for ( \leq 7 ) d</td>
<td>IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 1,000 U/h) for 48 h, or with abciximab IV bolus 40 U/kg (maximum 3,000 U), followed by an infusion 7 U/kg/h (maximum 800 U/h), adjusted to target APTT 50–70 s</td>
<td>No</td>
<td>150–325 mg/d</td>
<td>Tenecteplase</td>
<td>30</td>
<td>Enoxaparin: 109/2,037 (5.4) Lower-dose UFH + abciximab: 133/2,017 (6.6) UFH: 122/2,038 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Baird et al 2002</td>
<td>STE, receiving fibrinolysis</td>
<td>Enoxaparin 40 mg IV bolus then 40 mg SC q8h for 4 d</td>
<td>IV bolus 5,000 U, followed by 3,000 U per 24 h, adjusted to target APTT 2–2.5 times normal</td>
<td>No</td>
<td>75–300 mg/d</td>
<td>Streptokinase, anistreplase, or tPA (43% pre-hospital)</td>
<td>90</td>
<td>Enoxaparin: 9/149 (6.0) UFH: 16/151 (10.6)</td>
<td>Following the 4-d study period, patients at risk of left ventricular mural thrombosis (anterol MI) received 5,000 to 10,000-U IV boluses of UFH qph for 3 d; cardiac death Half-dose tenecteplase in patients receiving abciximab</td>
</tr>
<tr>
<td>Antman et al (ENTIRE TIMI 23) 2002</td>
<td>Age ( \geq 75 ) yr; symptom onset ( \leq 6 ) h; STE</td>
<td>Enoxaparin ( \pm 30 ) mg IV bolus, then 1 mg/kg SC q12h for 2–8 d</td>
<td>60 U/kg IV bolus, then 12 U/kg/h (with full-dose tenecteplase) or 40 U/kg IV bolus, then 7 U/kg/h (with half-dose tenecteplase + abciximab) for ( \geq 36 ) h, adjusted to target APTT 1.5–2.5 times control</td>
<td>No</td>
<td>( \geq 160 ) mg po or 250–500 mg IV followed by 100–325 mg/d</td>
<td>Tenecteplase</td>
<td>30</td>
<td>Enoxaparin: 10/324 (3.1) UFH: 5/159 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Cohen et al (TETAMI) 2003</td>
<td>STE MI and deemed unsuitable for fibrinolysis or primary PCI</td>
<td>Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for 2–8 d</td>
<td>70 U/kg IV bolus, then 15 U/kg/h for 2–8 d, adjusted to target APTT</td>
<td>Yes</td>
<td>100–325 mg/d</td>
<td>None</td>
<td>30</td>
<td>Enoxaparin: 42/604 (7.0) UFH: 41/620 (6.6)</td>
<td>Patients also randomized to receive tiroliban or placebo</td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features %</td>
<td>LMWH Regimen, Dose, Duration</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Blinded</td>
<td>Routine Aspirin Dose</td>
<td>Fibrinolytic(s)</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>Wallentin et al (ASSENT Plus) 2003</td>
<td>Symptom onset ≤ 6 h, STE or left BBB</td>
<td>Dalteparin 30 U/kg (maximum 2,500 U) IV bolus, then 90 U/kg SC, then 120 U/kg SC q12h for 4–7 d</td>
<td>IV bolus 4,000 U for weight ≤ 67 kg, 5,000 U for weight &gt; 67 kg, followed by infusion 800 U/h (≤ 67 kg) or 1,000 U/h (weight &gt; 67 kg) for 48 h, adjusted to target APTT 50–75 s</td>
<td>No</td>
<td>150–325 mg/d</td>
<td>tPA</td>
<td>30</td>
<td>Dalteparin: 9/221 (4.1)</td>
<td>UFH: 11/212 (5.2)</td>
</tr>
<tr>
<td>Zhang et al 2004</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Parnaparin 0.4 mL SC 12 h after lysis and then q12h for 7 d</td>
<td>100 U/kg IV bolus 12 h after lysis, followed by infusion 1,000 U/h for 3 d, adjusted to target APTT 1.5–2 times normal, then 7,500 U SC q12h for 4 d</td>
<td>No</td>
<td>75–150 mg/d</td>
<td>Yes, agents unknown</td>
<td>45</td>
<td>Parnaparin: 12/96 (12.5)</td>
<td>UFH: 14/90 (15.6)</td>
</tr>
<tr>
<td>Wallentin et al (ASSENT-3 PLUS) 2003</td>
<td>Symptom onset ≤ 6 h, STE or left BBB</td>
<td>Enoxaparin 30 mg IV bolus, then 1 mg/kg (maximum 100 mg for first 2 doses) SC q12h for ≤ 7 d</td>
<td>60 U/kg IV bolus (maximum 4,000 U), then 12 U/kg/h (maximum 1,000 U/h) for 48 h, adjusted to target APTT 50–70 s</td>
<td>No</td>
<td>150–325 mg initial, then 100–325 mg/d</td>
<td>Tenecteplase</td>
<td>30</td>
<td>Enoxaparin: 61/817 (7.5)</td>
<td>UFH: 49/818 (6.0)</td>
</tr>
<tr>
<td>Antman et al (EXTRACT-TIMI 25) 2006</td>
<td>Symptom onset ≤ 6 h, STE or left BBB</td>
<td>Enoxaparin 30 mg IV bolus for age &lt; 75 yr, then 1 mg/kg for age &lt; 75 yr or 0.75 mg/kg for age ≥ 75 yr (maximum 100 mg for age &lt; 75 yr or maximum 75 mg for age ≥ 75 yr for first 2 doses) SC q12h for ≤ 7 d</td>
<td>60 U/kg IV bolus (maximum 4,000 U), then 12 U/kg/h (maximum 1,000 U/h) for ≥ 48 h, adjusted to target APTT 50–70 s</td>
<td>Yes</td>
<td>150–325 mg po or 500 mg IV initial, then 75–325 mg/d</td>
<td>Tenecteplase (20%), tPA (55%), reteplase (6%), or streptokinas (20%)</td>
<td>30</td>
<td>Enoxaparin: 708/10,256 (6.9)</td>
<td>UFH: 765/10,233 (7.5)</td>
</tr>
</tbody>
</table>

For patients with an estimated creatinine clearance < 30 mL/min, dose was modified to 1 mg/kg q24h
selected components of the composite end points that were more favorable with enoxaparin as compared to UFH (in-hospital reinfarction and refractory ischemia) were investigator determined and subject to bias because of the open-label design. While the duration of antithrombin therapy also differed between the enoxaparin and UFH groups, the reduction in the primary efficacy end point was already evident at the end of the UFH infusion (48 h). One-year follow-up results demonstrated similar mortality rates among the enoxaparin and UFH groups: 8.1% vs 7.9% (RR, 1.03; 95% CI, 0.82 to 1.30; p = 0.79).193

The ASSENT-3 PLUS trial62 evaluated the feasibility, efficacy, and safety of prehospital treatment with either tenecteplase plus enoxaparin or tenecteplase plus UFH. The primary efficacy and efficacy plus safety end points were identical to those utilized in the main ASSENT-3 trial.84 Consistent with ASSENT-3,84 there was a trend toward a lower rate of the composite of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia in the enoxaparin group (14.2% vs 17.4%, p = 0.08). However, the lower rates of reinfarction (3.6% vs 5.9%, p = 0.028) and refractory ischemia (4.4% vs 6.5%, p = 0.067) were offset by a significantly higher rate of ICH (2.2% vs 0.97%, p = 0.048) and a tendency toward more major bleeding (4% vs 2.8%, p = 0.17). The risk for ICH and major bleeding in both ASSENT-3 and ASSENT-3 PLUS were mainly observed in patients > 65 years old;194 this may have been due in part to the initial non–weight-adjusted IV bolus of enoxaparin therapy (30 mg) and, despite a cap on the first two SC doses (1 mg/kg to a maximum of 100 mg), the lack of adjustment for renal function.

The finding of greater risk of ICH and major bleeding led to an omission of the initial IV enoxaparin bolus and an adjustment in the dose (to 0.75 mg/kg, to a maximum of 75 mg for the first two doses) in the EXTRACT-TIMI 25 trial.86 This was a double-blind, double-dummy comparison of enoxaparin (n = 10,256) administered for a median of 7 days (25–75 percentiles, 4.5 to 7.5 days) with UFH (n = 10,223) for at median of 2 days (25–75 percentiles, 2.0 to 2.2 days). Enoxaparin was administered as a 30 mg IV bolus followed by 1 mg/kg SC q12h for patients < 75 years of age (maximum, 100 mg for the first two SC doses) or 0.75 mg/kg without an IV bolus for patients ≥ 75 years (maximum, 75 mg for first two SC doses). Patients with known elevation in serum creatinine were excluded (> 2.5 mg/dL [220 μmol/L] in male patients and < 2.0 mg/dL [175 μmol/L] in female patients), and an adjustment in enoxaparin was made (1 mg/kg q24h) for those with an estimated creatinine clearance of < 30 mL/min. IV UFH was given as a 60 U/kg bolus (maximum, 4,000 U) followed by an infusion of 12 U/kg/h (maximum, 1,000 U/h) with a target APTT of 1.5 to 2 times control. The primary end point (30-day composite of all-cause mortality and nonfatal reinfarction) was significantly lower in the enoxaparin group (9.9% vs 12%; RR, 0.83; 95% CI, 0.77 to 0.90; p < 0.001). There were fewer deaths numerically in the enoxaparin group, but this was not statistically significant (6.9% vs 7.5%; RR, 0.92; 95% CI, 0.84 to 1.02; p = 0.11); nonfatal MI was significantly lower in the enoxaparin group (3.0% vs 4.5%; RR, 0.67; 95% CI, 0.58 to 0.77; p < 0.001). The benefit of enoxaparin was evident at 48 h (a time when both treatment groups were receiving active therapy) with a trend toward lower death and nonfatal MI (4.7% vs 5.2%; RR, 0.90; 95% CI, 0.80 to 1.01; p = 0.08). The apparent benefit of six fewer deaths and 15 fewer reinfarctions per 1,000 patients treated with enoxaparin compared with UFH was offset by a significant increase in 30-day major (including ICH; 2.1% vs 1.4%; RR, 1.53; 95% CI, 1.23 to 1.89; p < 0.001) and minor (2.6% vs 1.8%; RR, 1.41; 95% CI, 1.17 to 1.70; p < 0.001) bleeding. ICH rates were not significantly different in the enoxaparin and UFH groups (0.8% vs 0.7%; RR, 1.27; 95% CI, 0.92 to 1.75; p = 0.14). The net clinical benefit (eg, 30-day death, nonfatal MI, or major bleeding) remained in favor of enoxaparin (11% vs 12.8%; RR, 0.86; 95% CI, 0.80 to 0.93; p < 0.001). The RRR with enoxaparin on the primary end point (death or nonfatal recurrent MI) was greater in patients < 75 years old (n = 17,947; RRR, 20%) than ≥ 75 years old (n = 2,532; RRR, 6%), but the absolute risk differences were similar (2.0% and 1.5%, respectively).195 When compared with UFH, major bleeding was higher with enoxaparin in younger patients (1.1% vs 1.9%, p < 0.0001) but similar in the elderly (2.9% vs 3.3%, p = 0.53).195 ICH rates were similar in

Table 18—LMWH vs UFH for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.4)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>LMWH</th>
<th>UFH</th>
<th>OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>70% / 14,700 (4.8)</td>
<td>1,066 / 16,535 (6.4)</td>
<td>0.73 (0.67–0.81)</td>
<td>16 (3)</td>
<td>High</td>
</tr>
</tbody>
</table>

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younger patients (0.5% vs 0.7%, p = 0.06) and older patients (1.7% vs 1.6%, p = 0.85).195

As noted above, one trial195 examined the safety and efficacy of enoxaparin compared to IV UFH and the GP IIb/IIIa inhibitor tirofiban to placebo in a two-by-two factorial design in patients (n = 1,224) with acute STE MI who were ineligible for reperfusion (either fibrinolysis or primary PCI). Late arrival (79% and 66%) and unavailability of a catheterization laboratory/PCI not done routinely (61%) were the main reasons why fibrinolysis and primary PCI were not employed, respectively; however, even in patients apparently presenting within 12 h of symptom onset, late arrival remained the predominant reason for not providing reperfusion therapy (60% and 43%, respectively.) The primary efficacy end point rates of 30-day death, reinfarction, or recurrent angina were similar in the enoxaparin and UFH groups (15.7% vs 17.3%; OR, 0.89; 95% CI, 0.66 to 1.21); major bleeding rates were also similar (1.5% vs 1.3%; OR, 1.16; 95% CI, 0.44 to 3.02).

2.5 LMWH

Recommendations

2.5.1. For patients with acute STE MI, regardless of whether or not they receive reperfusion therapy, we recommend the use of reviparinux over no therapy (Grade 1B). Recommended dosing for reviparinux is 3,436 IU for < 50 kg, 5,153 IU for 50 to 75 kg, or 6,871 IU for > 75 kg q12h SC up to 7 days. For patients undergoing primary PCI, UFH should be used periprocedurally and reviparinux initiated 1 h after sheath removal.

2.5.2. For patients with acute STE MI receiving fibrinolytic therapy who have preserved renal function (≤ 2.5 mg/dL [220 μmol/L] in male patients and < 2.0 mg/dL [175 μmol/L] in female patients), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A). Recommended dosing for enoxaparin is for age < 75 years, 30-mg IV bolus followed by 1 mg/kg SC q12h (maximum, 100 mg for the first two SC doses); and for age ≥ 75 years, no IV bolus, 0.75 mg/kg SC q12h (maximum, 75 mg for the first two SC doses).

Fondaparinux

Fondaparinux, an indirect factor Xa inhibitor that selectively binds antithrombin and rapidly inhibits factor Xa, has been shown to have a better safety profile (with associated lower mortality) when compared to enoxaparin in ACS patients (n = 20,078) presenting without STE196 (see chapter by Harrington et al in this supplement). In a small, phase II study, patients (n = 333) with STE MI were treated with aspirin and alteplase and randomized to IV UFH (5,000 bolus followed by 1,000 U/h [4,000-U bolus followed by 800 U/h if ≤ 67 kg] to a target APTT of 50 to 75 s for 48 to 72 h), or to one of three different fondaparinux doses (low: 4 mg, or 6 mg if > 90 kg; medium: 8 mg, or 6 mg if < 60 kg or 10 mg if > 90 kg; high: 12 mg, or 10 mg if < 60 kg).197 The first fondaparinux dose was given IV prior to alteplase; subsequent doses were administered SC for 5 to 7 days. Coronary angiography was performed at 90 min and on days 5 to 7. TIMI flow grade 3 rates at 90 min and on days 5 to 7. TIMI flow grade 3 rates at 90 min were similar in the four treatment groups; among patients with TIMI 3 flow at 90 min and who did not undergo a coronary intervention (n = 155), a trend toward less reocclusion of the IRA on days 5 to 7 was observed with fondaparinux: 0.9% vs 7.0% with UFH (p = 0.065). The primary safety end point, the combined incidence of ICH and need for blood transfusion, was identical with fondaparinux and UFH (7.1%).

The OASIS-6 study168 was a randomized double-blind comparison of fondaparinux or control for up to 8 days in patients (n = 12,092) with STE MI (Tables 19–21). Randomization was stratified by indication for the use of UFH based on the investigator’s judgment; 5,658 patients were enrolled in stratum 1 (no indication for UFH), and 6,434 patients were enrolled in stratum 2 (indication for UFH; eg, intended use of fibrin-specific fibrinolytic, patients not eligible for fibrinolysis but eligible for antithrombotics, or those scheduled for primary PCI). Patients in stratum 1 were assigned to receive blinded fondaparinux (2.5 mg initially SC qd or matching placebo on subsequent days for up to 8 days [median, 8 days] or hospital discharge, if earlier). Patients in stratum 2 were assigned to receive either blinded fondaparinux (or matching placebo; initial dose IV and subsequent doses SC) for up to 8 days [median, 7 days] or hospital discharge. Those in the control group received IV UFH (bolus of 60 IU/kg [maximum, 4,000 IU for > 70 kg] followed by an infusion of 12 IU/kg/h [maximum, 1,000 IU/h for > 70 kg] for 24 to 48 h [median, 45 h]) to a target APTT of 1.5 to 2 times control for 24 to 45 h. Higher doses could be used during PCI according to whether the patient underwent primary PCI and received antecedent UFH with or without GP IIb/ IIIa inhibitor therapy168. From day 3 through day 9, all patients received either fondaparinux or placebo according to the original randomized assignment. Prerandomization IV UFH was used in 15% of patients in both treatment groups, including 6% of patients in stratum 1 (those subsequently believed
### Table 19—Randomized Trials of Fondaparinux vs Control or UFH in Suspected Acute MI: Clinical Description and Results (Section 2.5)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Fondaparinux Regimen, Dose, Duration</th>
<th>UFH Regimen, Dose, Duration</th>
<th>Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Reperfusion Therapy</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coussement et al (PENTALYSE) (^{167})</td>
<td>Age 21–75 yr, symptom onset ≤ 6 h, STE 100</td>
<td>IV bolus 4 mg (or 6 mg if weight &gt; 90 kg) or 8 mg (or 6 mg if weight &lt; 60 kg or 10 mg if weight &gt; 90 kg) or 12 mg (or 10 mg if weight &lt; 60 kg), then SC daily for 5–7 d</td>
<td>IV bolus 4,000 U for weight ≤ 67 kg, 5,000 U for weight &gt; 67 kg, followed by infusion 800 U/h (≤ 67 kg) or 1,000 U/h (weight &gt; 67 kg) for 48–72 h, adjusted to target APTT 50–75 s</td>
<td>No</td>
<td>150–325 mg/d</td>
<td>tPA</td>
<td>30</td>
<td>Fondaparinux: 6/241 (2.5)</td>
<td>UFH: 1/85 (1.2)</td>
</tr>
<tr>
<td>OASIS-6 Trial Group (^{166})</td>
<td>Symptom onset ≤ 12 h STE 100</td>
<td>2.5 mg (initial IV bolus for patients without an indication for UFH) SC daily for up to 8 d or hospital discharge</td>
<td>IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 1,000 U/h) for 48 h, adjusted to target APTT 1.5–2 times control (50%)</td>
<td>Yes</td>
<td>Yes, dose uncertain</td>
<td>Fibrinolysis (45%), primary PCI (29%), none (24%)</td>
<td>30</td>
<td>Fondaparinux: 470/6,036 (7.8)</td>
<td>Placebo: 321/2,835 (11.1)</td>
</tr>
</tbody>
</table>
not to have an indication for UFH). Postrandomization nonstudy UFH was used in approximately 11% of patients in both treatment groups, including 9% of patients in stratum 1.

The composite of death or MI was significantly reduced at 9 days (7.4% vs 8.9%; HR, 0.83; 95% CI, 0.73 to 0.94; p = 0.003), 30 days (primary outcome, 9.7% vs 11.2%; HR, 0.86; 95% CI, 0.77–0.96; p = 0.008), and at study end (3 to 6 months, 10.5% vs 11.5%; HR, 0.88; 95% CI, 0.79 to 0.97; p = 0.008) in the fondaparinux group compared to the control group. Consistent reductions in both death and reinfarction were observed at each of the three time points, with the reduction in deaths being statistically significant throughout (eg, at day 30: 7.8% vs 8.9%; HR, 0.87; 95% CI, 0.77 to 0.98; p = 0.03). Within stratum 1 (those without an indication for UFH), patients receiving fondaparinux had a significantly lower death or reinfarction rate when compared with placebo (eg, at day 30: 11.2% vs 14%; HR, 0.79; 95% CI, 0.68 to 0.92); in stratum 2 (those with an indication for UFH), there was no difference between fondaparinux and UFH (eg, at day 30: 8.3% vs 8.7%; HR, 0.96; 95% CI, 0.81 to 1.13). Less impressive differences may in part be due to an apparent increase in death or reinfarction among patients in stratum 2 who underwent primary PCI (n = 3768) as their initial reperfusion treatment and received fondaparinux (median, 5.4 days) [eg, at day 30: 6.1% vs 5.1%; HR, 1.20; 95% CI, 0.91 to 1.57; p = 0.19]; in contrast, those who did not undergo primary PCI (n = 2,666, including those who received fibrinolysis and those who did not) showed a trend toward benefit with fondaparinux as compared to UFH (eg, at day 30: 11.5% vs 13.8%; HR, 0.82; 95% CI, 0.66 to 1.02; p = 0.08).

Among those patients (n = 2,867) who did not receive any initial reperfusion therapy, fondaparinux (median, 6.6 days) was superior to control (placebo or UFH) in reducing 30-day death or reinfarction (12.2% vs 15.1%, p < 0.05). Similarly, among those patients who received fibrinolytic therapy (n = 5,436), fondaparinux (median, 6.3 days) was significantly better than control (placebo or UFH; 10.9% vs 13.6%, p < 0.05). The majority of patients receiving fibrinolysis received a non–fibrin-specific agent (eg, streptokinase or urokinase; n = 4,561); among the subgroup of patients in stratum 2 (with an indication for UFH) who received a fibrin-specific lytic (n = 855), there was no apparent benefit of fondaparinux.198 There was a nonsignificant trend toward fewer severe hemorrhages (using a modified TIMI major bleeding definition) with fondaparinux compared with the control group (placebo or UFH) at 9 days (1% vs 1.3%; HR, 0.77; 95% CI, 0.55 to 1.08; p = 0.13). Surprisingly, lower rates were observed for severe hemorrhage (44 vs 28 cases, p = 0.06) and for major bleeds (57 vs 39 cases, p = 0.07) with fondaparinux compared with placebo (in stratum 1), although this finding may be due to chance. In stratum 2, the rates of severe and major bleeds were similar in the fondaparinux and UFH groups (1.1% vs 1.1%, and 2.1% vs 2.3%, respectively). The rates of ICH were similar in the two groups (0.2% vs 0.2%).

Consistent with the experience in non-STE ACS196 (see chapter by Harrington et al in this supplement) in patients undergoing primary PCI, there was a higher rate of guiding catheter thrombosis (0 vs 22 cases, p < 0.001) and more coronary complications (abrupt coronary artery closure, new angiographic thrombus, catheter thrombus, no reflow, dissection, or perforation; 225 vs 270 cases, p = 0.04) with fondaparinux. Among the patients who received UFH prior to primary PCI (n = 496), these differences were not as striking (eg, catheter thrombus in two patients receiving fondaparinux compared to no patients receiving UFH). In the 231 fondaparinux patients who underwent a PCI (other than primary) in hospital (where UFH was recom-

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**Table 20**—Fondaparinux vs Control for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.5)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>No. of Deaths/Patients (%)</th>
<th>OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>470/6,036 (7.8)</td>
<td>321/2,835 (11.1)</td>
<td>0.66 (0.57–0.77)</td>
<td>High</td>
</tr>
</tbody>
</table>

**Table 21**—Fondaparinux vs UFH for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.5)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>No. of Deaths/Patients (%)</th>
<th>OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>476/6,277 (7.6)</td>
<td>220/3,306 (6.7)</td>
<td>1.15 (0.98–1.36)</td>
<td>High</td>
</tr>
</tbody>
</table>
mended prior to the procedure), there were no catheter-related thrombi seen. However, the appropriate dosing of UFH in addition to fondaparinux in order to avoid catheter-related complications but also bleeding remains uncertain.

2.6 Fondaparinux

Recommendations

2.6.1. For patients with acute STE MI and not receiving reperfusion therapy, we recommend fondaparinux over no therapy (Grade 1A). Recommended dosing for fondaparinux is 2.5 mg IV for the first dose and then SC qd up to 9 days. [Grade 1B].

2.6.2. For patients with acute STE MI receiving fibrinolytic therapy and thought not to have an indication for anticoagulation, we recommend fondaparinux over no therapy (2.5 mg IV for the first dose and then SC qd up to 9 days) [Grade 1B].

2.6.3. For patients with acute STE MI receiving fibrinolytic therapy and thought to have an indication for anticoagulation, we recommend fondaparinux (2.5 mg IV for the first dose and then SC qd up to 9 days) could be used as an alternative to UFH (Grade 2B).

2.6.4. For patients with acute STE MI and undergoing primary PCI, we recommend against using fondaparinux (Grade 1A).

2.7 Direct Thrombin Inhibitors

Direct thrombin inhibitors have undergone extensive evaluation in acute coronary syndromes, including STE MI patients receiving fibrinolysis (Tables 22, 23). A metaanalysis\(^\text{199}\) included individual patient data (n = 9,947) from five trials (≥ 200 patients and ≥ 100 control subjects) evaluating argatroban (n = 1,200),\(^\text{200}\) hirudin (n = 8,343),\(^\text{82,83,201}\) and bivalirudin (hirulog; n = 404)\(^\text{202}\) compared to UFH (IV 5,000-IU bolus followed by 1,000 IU/h, range 72 h to 7 days, except in one study where patients received a placebo bolus and SC UFH at 12,500 IU bid\(^\text{201}\)). Overall, there was a significant reduction in the end point of recurrent MI with direct thrombin inhibitors compared with IV UFH (2.5% vs 3.4%; OR, 0.75; 95% CI, 0.59 to 0.94). However, this reduction was seen with hirudin and bivalirudin and not with univalent agents. Further, overall mortality with adjunctive direct thrombin inhibitor was similar (4.1% vs 3.9%; OR, 1.07; 95% CI, 0.88 to 1.31) and the combined end point of death and recurrent MI was not significantly reduced (6.3% vs 6.9%; OR, 0.91; 95% CI, 0.77 to 1.06).

Overall, 11 randomized trials of patients (n = 35,970) with and without STE ACS were included in the metaanalysis\(^\text{199}\); there was no excess of ICH with direct thrombin inhibitors compared with UFH (0.11% vs 0.16%; OR, 0.72; 95% CI, 0.42 to 1.23; p = 0.22). Direct thrombin inhibitors appeared to be associated with a lower risk of major bleeding overall during treatment (1.9% vs 2.3%; OR, 0.75; 95% CI, 0.65 to 0.87; p < 0.001).

In addition to the studies in the metaanalysis,\(^\text{199}\) the large international HERO-2 trial\(^\text{167}\) compared IV bivalirudin and IV UFH for at least 48 h after streptokinase in STE MI patients (n = 17,073). Bivalirudin was administered as a 0.25 mg/kg bolus followed by an infusion of 0.5 mg/kg/h for the first 12 h and then 0.25 mg/kg/h for the subsequent 36 h; APTTs were measured at 12 h and 24 h, but dose reduction was not permitted after the 12-h APTT measurement unless there was major bleeding. If the APTT was > 150 s, it was to be measured again at 18 h, at which time the dose of bivalirudin was reduced if the APTT remained > 150 s; after 24 h, the dose could be reduced by a third if there was major bleeding or if the APTT was > 120 s. UFH was administered as a 5,000-U bolus followed by 800 U/h (< 80 kg) or 1,000 U/h (≥ 80 kg), and a target APTT of 50 to 75 s. Bivalirudin did not reduce the primary 30-day mortality end point (10.8% vs 10.9%; OR, 0.99; 95% CI, 0.90 to 1.09; p = 0.85). There was a significantly lower rate of reinfarction at 96 h (1.6% vs 2.3%; OR, 0.70; 95% CI, 0.56 to 0.87; p = 0.001) and during the index hospitalization (2.8% vs 3.6%; OR, 0.78; 95% CI, 0.66 to 0.93; p = 0.005). Rates of severe bleeding (0.7% vs 0.5%; OR, 1.46; 95% CI, 0.98 to 2.19; p = 0.07) and ICH (0.6% vs 0.4%; OR, 1.48; 95% CI, 0.94 to 2.32; p = 0.09) tended to be higher with the use of bivalirudin; major bleeding (1.4% vs 1.1%; OR, 1.32; 95% CI, 1.00 to 1.74; p = 0.05) and minor bleeding (12.8% vs 9.0%; OR, 1.47; 95% CI, 1.34 to 1.62; p < 0.0001) were significantly higher.

Direct thrombin inhibitors have been studied as an alternative to UFH with or without GP IIb/IIIa inhibitors in patients undergoing PCI, including those with a recent ACS\(^\text{203–211}\); however, there is currently no data available to support their use as adjunctive therapy to primary PCI in STE MI. Direct thrombin inhibitors have also been used in patients with heparin-induced thrombocytopenia (HIT) undergoing PCI.\(^\text{212–214}\) Direct thrombin inhibitors could also be utilized as an alternative to UFH in the setting of STE MI when HIT is present or suspected (see chapter by Warkentin et al in this supplement). Given the clinical trial experience to date, hirudin could be used with tPA and tPA derivatives, and bivalirudin could be used with streptokinase.
### Table 22—Randomized Trials of Direct Thrombin Inhibitors vs UFH in Suspected Acute MI: Clinical Description and Results (Section 2.6)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Direct Thrombin Inhibitor Regimen, Dose, Duration</th>
<th>UFH Regimen, Dose, Duration Blinded</th>
<th>Routine Aspirin Dose</th>
<th>Reperfusion Therapy</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman et al (TIMI 9A)1994</td>
<td>Symptom onset ≤ 12 h; STE 100</td>
<td>2.5 mg (initial IV bolus for patients without an indication for UFH) SC daily for up to 8 d or hospital discharge</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h (weight &lt; 80 kg) or 1,300 U/h (weight ≥ 80 kg) for 72-120 h, adjusted to target APTT 60-90 s</td>
<td>Yes 150-325 mg/d</td>
<td>tPA or streptokinase</td>
<td>30</td>
<td>Unknown</td>
<td>Study stopped prematurely due to excessive ICH after 757 patients enrolled</td>
</tr>
<tr>
<td>GUSTO Ha Investigators 1994</td>
<td>Symptom onset &lt; 12 h; STE, ST-segment depression or T-wave inversion</td>
<td>Hirudin 0.6 mg/kg IV bolus, followed by 0.2 mg/kg/h infusion for 72-120 h, maintaining APTT &lt; 150 s</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h (weight &lt; 80 kg) or 1,300 U/h (weight ≥ 80 kg) for 72-120 h, adjusted to target APTT 60-90 s</td>
<td>Yes Yes, dose uncertain</td>
<td>tPA or streptokinase for STE</td>
<td>30</td>
<td>Unknown</td>
<td>Study stopped prematurely due to excessive ICH after 2,564 patients enrolled</td>
</tr>
<tr>
<td>Neuhaus et al (HIT-III) 1994</td>
<td>Symptom onset ≤ 6 h; STE 100</td>
<td>Hirudin 0.4 mg/kg IV bolus, followed by 0.15 mg/kg/h infusion for 72-120 h, maintaining APTT 2-3.5 times control</td>
<td>IV bolus 70 U/kg, followed by 15 U/kg/h infusion for 48-72 h, maintaining APTT 2-3.5 times control</td>
<td>Yes 250 mg initial, 100-500 mg/d</td>
<td>tPA In-hospital</td>
<td>30</td>
<td>Hirudin: 13/148 (8.8) UFH: 6/154 (3.9)</td>
<td>Study stopped prematurely due to excessive ICH in the hirudin vs UFH group after 302 patients enrolled</td>
</tr>
<tr>
<td>GUSTO Hb Investigators 1996</td>
<td>Symptom onset &lt; 12 h; STE, ST-segment depression or T-wave inversion</td>
<td>Hirudin 0.1 mg/kg IV bolus, followed by 0.1 mg/kg/h infusion for 72-120 h, adjusted to target APTT 60-85 s</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h for 72-120 h, adjusted to target APTT 60-85 s</td>
<td>Yes Yes, dose uncertain</td>
<td>tPA or streptokinase for STE</td>
<td>30</td>
<td>Hirudin: 122/2,075 (5.9) UFH: 127/2,056 (6.2)</td>
<td>Among STE patients only</td>
</tr>
<tr>
<td>Antman et al (TIMI 9B) 1996</td>
<td>Symptom onset ≤ 12 h; STE or left BBB</td>
<td>Hirudin 0.1 mg/kg IV bolus (maximum 15 mg), followed by 0.1 mg/kg/h infusion (maximum 15 mg/h) for 96 h, adjusted to target APTT 55-85 s</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h for 96 h, adjusted to target APTT 55-85 s</td>
<td>Yes 150-325 mg/d</td>
<td>tPA or streptokinase</td>
<td>30</td>
<td>Hirudin: 92/1,511 (6.1) UFH: 76/1,491 (5.1)</td>
<td></td>
</tr>
<tr>
<td>White et al (HERO) 1997</td>
<td>Symptom onset ≤ 12 h; STE 100</td>
<td>Bivalirudin (hirulog) 0.125 mg/kg IV bolus, followed by 0.25 mg/kg/h for 12 h then 0.125 mg/kg/h or 0.25 mg/kg IV bolus, followed by 0.5 mg/kg/h for 12 h then 0.25 mg/kg/h, without downward adjustment ≤ 24 h except for bleeding</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h (weight &lt; 80 kg) or 1,200 U/h (weight ≥ 80 kg) for 60 h, with adjustment at 11 and 24 h to target APTT (not specified)</td>
<td>Yes 150-325 mg/d</td>
<td>Streptokinase</td>
<td>35</td>
<td>Bivalirudin (hirulog): If clinically indicated (e.g., APTT &gt; 120 s or excessive oozing) &gt; 24 h of dosing, infusions reduced by one third; combining low (8/136) and high (6/136) dose bivalirudin (hirulog)</td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features %</td>
<td>Direct Thrombin Inhibitor Regimen, Dose, Duration</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Routine Aspirin Dose</td>
<td>Reperfusion Therapy</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>Behar et al (ARGAMI-2) (^{200}) 1998</td>
<td>STE</td>
<td>Argatroban 20 mg/kg IV bolus followed by 2 mg/kg/min infusion or 60 mg/kg IV bolus followed by 4 mg/kg/min infusion for 72 h, target APTT uncertain</td>
<td>IV bolus 5,000 U, followed by 1,000 U/h for 72 h, target APTT uncertain</td>
<td>Yes, dose uncertain</td>
<td>Streptokinase (50%) or tPA (50%)</td>
<td>30</td>
<td>Unknown</td>
<td>Low-dose argatroban arm discontinued after 199 patients (609 patients in total) due to lack of efficacy</td>
</tr>
<tr>
<td>Neuhaus et al (HIT-4) (^{201}) 1999</td>
<td>Age 18–75 yr; symptom onset &lt; 6 h; STE 100</td>
<td>Lepirudin 0.2 mg/kg IV bolus, followed by 0.5 mg/kg SC bid for 5–7 days, adjusted to target APTT 2 times control</td>
<td>IV bolus 70 U/kg, followed by 15 U/kg/h infusion for 48–72 h, maintaining APTT 2–3.5 times control</td>
<td>Yes</td>
<td>300 mg initial, 100–200 mg/d</td>
<td>Streptokinase</td>
<td>30</td>
<td>Lepirudin: 41/603 (6.8) Streptokinase: 39/605 (6.4)</td>
</tr>
<tr>
<td>HERO-2 Trial Investigators (^{270}) 2001</td>
<td>Symptom onset &lt; 6 h; STE or left BBB</td>
<td>Bivalirudin 0.25 mg/kg IV bolus, followed by 0.5 mg/kg/h for 12 h then 0.25 mg/kg/h for 36 h, without downward adjustment ≤ 12 h except for major bleeding</td>
<td>IV bolus 5,000 U, followed by 800 U/h (weight &lt; 80 kg) or 1,000 U/h (weight ≥ 80 kg) for ≥ 48 h, adjusted to target APTT of 50–75 s after 12 h</td>
<td>No</td>
<td>150–325 mg/d</td>
<td>Streptokinase</td>
<td>30</td>
<td>Bivalirudin: 919/8,516 (10.8) Streptokinase: 931/8,357 (10.9) OR 0.99 (95% CI 0.90–1.09)</td>
</tr>
</tbody>
</table>
2.7 Direct Thrombin Inhibitors

Recommendation

2.7.1. For patients with acute STE MI treated with streptokinase, we suggest clinicians not use bivalirudin as an alternative to UFH (Grade 2B).

Underlying values and preferences: This recommendation places a relatively higher value on avoiding excess of major bleeding and a relatively lower value on avoiding reinfarction. Recommended dosing for bivalirudin is 0.25 mg/kg IV bolus followed by an infusion of 0.5 mg/kg/h for the first 12 h and then 0.25 mg/kg/h for the subsequent 36 h; APTTs should be measured at 12 h and 24 h with potential dose reductions as noted (see previous text).

2.8 GP IIb/IIIa Inhibitors

Platelet GP IIb/IIIa receptor inhibitors have been shown to be effective and safe in reducing the ischemic complications of PCI and reducing the composite of death or MI among patients presenting with ACS without STE.215,216 The success of these agents in these groups of patients has led to a number of investigations using GP IIb/IIIa inhibitors in acute STE MI. Studies evaluating the use of GP IIb/IIIa inhibitors as the sole means of reperfusion (ie, without fibrinolysis or in conjunction with primary PCI) do not suggest that restoration of TIMI 3 flow occurs in a sufficient proportion of patients to support their use in isolation.217 Thus, GP IIb/IIIa inhibitors have been combined with fibrinolytic therapy and as an adjunct to a strategy of primary PCI.

Initial trials218–221 (Table 24) were performed with full doses of both fibrinolytic agents and GP IIb/IIIa inhibitors; and while these trials uniformly showed improvement in the angiographic or ECG measures of reperfusion, significant concerns were raised about bleeding risks with this combination therapy, especially without any indication of improved clinical outcomes. This concern led to the design of additional phase II trials evaluating the combination of partial or “half”-dose fibrinolytic therapy with GP IIb/IIIa inhibitors.222–226 Again, these studies demonstrated higher TIMI 3 flow rates in the IRA and improved ECG measures of reperfusion when compared with fibrinolysis alone. However, even lower doses of streptokinase led to excessive bleeding.221,222

The Global Use of Strategies to Open Occluded Coronary Arteries 5 trial227 randomized STE MI patients (n = 16,588) within 6 h of symptom onset to receive standard dose of reteplase (10 U + 10 U, 30 min apart) or a combination of abciximab (0.25 mg/kg bolus, 0.125 μg/kg/min infusion [maximum, 10 μg/min] for 12 h with half-dose reteplase (5 U + 5 U 30 min apart). Patients receiving half-dose reteplase and abciximab received a lower dose of IV UFH (60 U/kg [5,000-U maximum] followed by 7 U/kg/h) than those receiving standard-dose reteplase (5,000-U bolus followed by 1,000 U/h or 800 U/h if < 80 kg). The primary end point of 30-day mortality was similar in the standard-dose reteplase and combination half-dose reteplase plus abciximab-treated patients (5.9% vs 5.6%; OR, 0.95; 95% CI, 0.83 to 1.08; p = 0.43). Bleeding (eg, severe 0.5% vs 1.1%; OR, 2.14; 95% CI, 1.48 to 3.09; p < 0.0001; and moderate 1.8% vs 3.5%; OR, 1.97; 95% CI, 1.61 to 2.41; p < 0.0001) and the need for any transfusion (4% vs 5.7%; OR, 1.46; 95% CI, 1.26 to 1.69; p < 0.0001) were significantly higher with combination therapy. There was no difference in the incidence of nonfatal disabling stroke (0.3% vs 0.2%, p = 0.37) or any stroke (0.9% vs 1.0%, p = 0.55) between the two groups. However, patients > 75 years old receiving combination therapy had a doubling of the risk for ICH (1.1% vs 2.1%; OR, 1.91; 95% CI, 0.95 to 3.84; p = 0.069); indeed, age showed a significant interaction with treatment effect with a lower risk for ICH with combination therapy for younger patients and a higher risk for the elderly.228 Rates of reinfarction (3.5% vs 2.3%, p < 0.0001) and recurrent ischemia (12.8% vs 11.3%, p < 0.0001) were significantly reduced with combination therapy. However, despite the reduction in reinfarction, mortality remained similar in the reteplase alone and combination therapy arms at 1-year follow-up (8.38% vs 8.38%; HR, 1.00; 95% CI, 0.90 to 1.11; p > 0.99).229

Table 23—Direct Thrombin Inhibitors vs UFH for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.6)*

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Direct Thrombin Inhibitor</th>
<th>UFH</th>
<th>OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.132/13,664 (8.3)</td>
<td>1.117/13,356 (8.4)</td>
<td>0.99 (0.91–1.08)</td>
<td>1 (6)</td>
<td>High</td>
</tr>
</tbody>
</table>

*Includes all randomized trials including patients with STE MI meeting inclusion criteria for the quantitative review by The Direct Thrombin Inhibitor Trialists’ Collaborative Group plus the study by the HERO-2 Trial Investigators.
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Reperfusion Therapy</th>
<th>GP IIb/IIIa Inhibitor Regimen, Dose, Duration</th>
<th>Routine Antiplatelet Therapy, Dose</th>
<th>UFH Regimen, Dose, Duration</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleiman et al (TAMI S)(^\text{2s}) 1993</td>
<td>Age ≤ 76 yr, symptom onset ≤ 6 h, STE or LBBB with ST-segment changes (inferior or anterior)</td>
<td>tPA 100 mg over 3 h (80 mg in the 1st hr with 16% of the dose as an IV bolus, followed by 20 mg for each of the subsequent 2 h)</td>
<td>Abciximab 0.10, 0.15, 0.20, and 0.25 mg/kg IV infusion started 3, 6, and 15 h after start of tPA</td>
<td>No</td>
<td>Aspirin 160–325 mg/d</td>
<td>5,000 U IV bolus, followed by infusion 1,000 U/h beginning 90 min after initiation of tPA or 2,500 U IV bolus, followed by infusion 500 U/h beginning at the completion of tPA for patients receiving abciximab at 3 h and 6 h post-tPA, target APTT 65–80 s</td>
<td>In-hospital</td>
<td>Abciximab: 1/60 (1.7) Control: 0/10 (0)</td>
</tr>
<tr>
<td>Ohman et al (IMPACT-AMI)(^\text{3,4}) 1997</td>
<td>Age ≤ 75 yr, symptom onset ≤ 6 h, STE or left BBB with ST-segment changes (inferior or anterior)</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min)</td>
<td>Eptifibatide 36, 72, 108, 135, and 180 μg/kg IV boluses, followed by 0.2, 0.4, 0.6, and 0.75 μg/kg/min infusions for 24 h</td>
<td>No</td>
<td>Aspirin 325 mg/d</td>
<td>40 U/kg bolus, followed by infusion 15 U/kg/h, adjusted to maintain an APTT of 2–2.5 times control</td>
<td>In-hospital</td>
<td>Eptifibatide: 10/125 (8.0) Control: 4/55 (7.3)</td>
</tr>
<tr>
<td>PARADIGM(^\text{5,6}) 1998</td>
<td>Age ≤ 75 yr, symptom onset ≤ 12 h, STE</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or streptokinase 1.5 × 10^6 U over 1 h</td>
<td>Lamifiban 300 and 400 μg boluses followed by 1.0, 1.5, and 2.0 μg/min infusions for 24 and 48 h</td>
<td>Yes</td>
<td>Aspirin 160–325 mg/d</td>
<td>For tPA: 5,000 U IV bolus, followed by infusion 1,000 U/h for 24 h, to maintain an APTT of 60–85 s for streptokinase, no UFH in the first 24 h</td>
<td>In-hospital</td>
<td>Lamifiban: 5/236 (2.1) Placebo: 3/117 (2.6)</td>
</tr>
<tr>
<td>Ronner et al(^\text{7}) 2000</td>
<td>Symptom onset ≤ 6 h, STE</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h</td>
<td>Eptifibatide 180 μg/kg IV bolus, followed by 0.75, 1.33, and 2.0 μg/kg/min infusions for 72 h</td>
<td>Yes</td>
<td>Aspirin 250–500 mg, followed by ≥ 80 mg/d</td>
<td>None</td>
<td>30</td>
<td>Eptifibatide: 5/119 (4.2) Placebo: 4/62 (6.5)</td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Reperfusion Therapy</td>
<td>GP IIb/IIIa Inhibitor Regimen, Dose, Duration Blinded</td>
<td>Routine Antiplatelet Therapy, Dose</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
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<tr>
<td>Antman et al (TIMI 14) 1999</td>
<td>Age ≤ 75 yr, symptom onset ≤ 12 h, STE</td>
<td>tPA 100 mg over 90 min (15 mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min) or reduced-dose tPA 20, 35, 50, and 65 mg given as boluses (20, 35, and 50 mg) or bolus + infusion (varying doses over varying time intervals 30–60 min) or streptokinase 0.5, 0.75, 1.25 and 1.5 × 10^6 U over 1 h</td>
<td>Abciximab 0.25 mg/kg (or 0.3 mg/kg) IV bolus, followed by a 0.125 μg/kg min infusion for 12 h started after angiography and prior to PCI</td>
<td>No</td>
<td>Aspirin 150–325 mg oral or 250–500 mg IV</td>
<td>For full-dose tPA: 70 U/kg IV bolus (maximum 4,000 U), followed by infusion 15 U/kg/h (maximum 1,200 U/h); for reduced dose tPA or streptokinase: 60 U/kg IV bolus (maximum 4,000 U), followed by infusion 7 U/kg/h (maximum 500 U/h), heparin infusions adjusted to target APTT 50–70 s</td>
<td>30</td>
<td>tPA: 5/163 (3.1) Abciximab alone: 0/32 (0) Abciximab + reduced dose streptokinase: 5/143 (3.5) Abciximab + reduced dose tPA: 13/339 (3.8) In one subgroup (n = 48), patients received tPA 50 mg (15-mg bolus followed by 35 mg over 60 min) and a higher bolus of abciximab (0.3 mg/kg) with lower UFH dosing (30 U/kg IV [maximum 2,000 U], followed by infusion 4 U/kg/h [maximum 400 U]).</td>
</tr>
<tr>
<td>Antman et al (TIMI 14) 2000</td>
<td>Age ≤ 75 yr, symptom onset ≤ 12 h, STE</td>
<td>Retepase 10 × 10^6 U boluses given 30 min apart or reteplase 5 × 10^6 U boluses given 30 min apart or 10 × 10^6 U and 5 × 10^6 U boluses given 30 min apart</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started after angiography and prior to PCI</td>
<td>No</td>
<td>Aspirin 150–325 mg oral or 250–500 mg IV</td>
<td>For full-dose reteplase: 70 U/kg IV bolus (maximum 4,000 U), followed by infusion 15 U/kg/h (maximum 1,200 U/h); for reduced dose reteplase: 60 U/kg IV bolus (maximum 4,000 U), followed by infusion 7 U/kg/h (maximum 500 U/h), heparin infusions adjusted to target APTT 50–70 s</td>
<td>30</td>
<td>Retepase: 3/102 (2.9) Abciximab + reduced dose reteplase (5 × 10^6 U + 5 × 10^6 U): 2/105 (1.9) Abciximab + reduced dose reteplase (10 × 10^6 U): 892 (8.7)</td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Reperfusion Therapy</td>
<td>GP IIIb/IIIa Inhibitor Regimen, Dose, Duration Blinded</td>
<td>Routine Antiplatelet Therapy, Dose</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>SPEED224 2000</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Reteplase 5, 7.5 or 10 × 10 U bolus followed by no bolus or 2.5, 5 or 10 × 10^6 U bolus given 30 min later</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started in emergency department</td>
<td>No</td>
<td>Aspirin 150–325 mg po or 250–500 mg IV, followed by 80–325 mg/d po</td>
<td>For full-dose reteplase: 70 U/kg IV bolus (maximum 5,000 U); for reduced dose reteplase: 40 or 60 U/kg IV bolus (maximum 4,000 U), followed by additional weight-adjusted bolus doses or a continuous infusion during angiography and PCI, adjusted to maintain an ACT ≥ 200 s; if continued beyond sheath removal, target APTT 50–70 s</td>
<td>30</td>
<td>Retplase: 6/109 (5.5)</td>
</tr>
<tr>
<td>Giugliano et al (INTEGRITI) 2003</td>
<td>Age ≥ 75 yr, symptom onset ≤ 6 h, STE</td>
<td>Tenecteplase full-dose (0.53 mg/kg) or reduced-dose (0.27 or 0.40 mg/kg)</td>
<td>Eptifibatide 180 μg/kg IV bolus, followed by 90 μg/kg or 150 μg/kg IV bolus 10 min later, followed by infusion 2.0 μg/kg/min infusions for 18–24 h post PCI or 40–48 h in patients not undergoing early PCI</td>
<td>No</td>
<td>Aspirin 162–325 mg oral or 150–500 mg IV, followed by oral daily</td>
<td>60 U/kg IV bolus (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 500 U/h) for full-dose tenecteplase or 7 U/kg/h (maximum 400 U/h) for low-dose tenecteplase, adjusted to target APTT 50–70 s</td>
<td>30</td>
<td>Full-dose tenecteplase: 6/118 (5.1)</td>
</tr>
<tr>
<td>Brener et al (RAPPORT) 1998</td>
<td>Symptom onset ≤ 12 h, STE or ne new left BBB</td>
<td>Primary PCI (balloon angioplasty or directional atherectomy); stents allowed for large residual dissections with &gt; 50% stenosis and for abrupt or threatened vessel closure</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.25 μg/kg/min (maximum 10 μg/min) infusion for 12 h started before PCI (≥ 30 min in 20%)</td>
<td>Yes</td>
<td>Aspirin (dose unknown); ticlopidine in 15% of patients (who received stents)</td>
<td>IV bolus 100 U/kg, followed by additional weight-adjusted doses to maintain an ACT &gt; 300 s during the procedure and up to maximum 48 h, target APTT 60–85 s</td>
<td>30</td>
<td>Abciximab: 6/241 (2.5)</td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Reperfusion Therapy</td>
<td>GP IIb/IIIa Inhibitor Regimen, Dose, Duration Blinded</td>
<td>Routine Antiplatelet Therapy, Dose</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>Neumann et al (ISAR-2) 2000</td>
<td>Patients undergoing stent placement ≤ 48 h of STE MI</td>
<td>Fibrinolysis (22%)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by 0.125 μg/kg/min infusion for 12 h started before PCI</td>
<td>Aspirin, dose unknown; ticlopidine 250 mg bid in 92% of patients who received stents</td>
<td>IV bolus 5,000 U then additional 2,500 U for patients receiving abciximab (50%) or 10,000 U followed by infusion 1,000 U/h (50%) for 12 h</td>
<td>30</td>
<td>Abciximab: 4/201 (2.0) Placebo: 8/200 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Montalescot et al (ADMIRAL) 2001</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Primary PCI</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started immediately and before angiography (including 26% in the mobile ICU or emergency department)</td>
<td>Aspirin 324 mg po or 250 mg IV, then 325 mg/d; ticlopidine 300 mg, then 250 mg bid or 75 mg d, respectively in patients who received stents</td>
<td>IV bolus 70 U/kg (maximum 7,000 U), followed by additional weight-adjusted doses to maintain an ACT ≥ 200 s during the procedure and 7 U/kg/h after until repeat angiogram at 24 h, target APTT 1.5–2 times control</td>
<td>30</td>
<td>Abciximab: 5/149 (3.4) Placebo: 10/151 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Stone et al (CADILLAC) 2002</td>
<td>Symptoms onset ≤ 12 h, STE or left BBB (88%) or other ECG findings if high-grade angiographic stenosis and associated regional wall motion abnormalities (12%)</td>
<td>Primary PCI (stent [50%] or angioplasty [50%])</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started after angiography and prior to PCI</td>
<td>Aspirin 324 mg po or 250 mg IV, then 325 mg/d; ticlopidine 300 mg, then 250 mg bid or 75 mg d, respectively in patients who received stents</td>
<td>IV to achieve an ACT ≥ 350 s or 200–300 s in patients receiving abciximab</td>
<td>30</td>
<td>Abciximab: 20/1,052 (1.9) Placebo: 24/1,030 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Petronio et al 2002</td>
<td>Symptoms onset ≤ 24 h, persistent STE &gt; 1 mm limb leads, &gt; 2 mm precordial leads) &gt; 90 min (mean 8.5 h) before fibrinolysis and IRA stenosis &gt; 60% and TIMI flow grade &lt; 3</td>
<td>tPA (88%) or streptokinase (12%)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h (given a mean of 6.4 ± 7.2 h after fibrinolysis)</td>
<td>Aspirin 300 mg daily, ticlopidine 250 mg bid for 1 wk followed by 250 mg/d in patients who received stents</td>
<td>IV bolus 70 U/kg, followed by infusion 10 U/kg/h (mean 12.7 ± 7.1 h), target APTT 50–70 s</td>
<td>30</td>
<td>Abciximab: 1/44 (2.3) Placebo: 4/45 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Reperfusion Therapy</td>
<td>GP IIb/IIIa Inhibitor Regimen, Dose, Duration</td>
<td>Routine Antiplatelet Therapy, Dose</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
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<tr>
<td>Zorman et al 235 2002</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Primary PCI (angioplasty)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started immediately (33%) or prior to angioplasty (33%)</td>
<td>Aspirin 250–500 mg/d</td>
<td>IV bolus 70 U/kg</td>
<td>In-hospital</td>
<td>Abciximab: 4/113 (3.6) Control: 5/51 (9.8)</td>
<td></td>
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<tr>
<td>Antoniucci et al 236 2003</td>
<td>Symptom onset ≥ 6 h or 6–24 h if evidence of ongoing ischemia, STE</td>
<td>Primary PCI (stenting)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started prior to PCI</td>
<td>Aspirin 250 mg IV or 325 mg orally, followed by 325 mg/d; ticlopidine 500 mg or clopidogrel 300 mg, then 250 mg bid or 75 mg/d, respectively</td>
<td>IV bolus 70 U/kg to achieve ACT ≥ 300 s or 200–300 s in patients receiving abciximab, followed by infusion for 48 h or 12 h in patients receiving abciximab</td>
<td></td>
<td>Abciximab: 7/200 (3.5) Control: 5/200 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Petronio et al 237 2003</td>
<td>Symptom onset ≤ 6 h, STE and IRA occlusion with thrombus</td>
<td>Primary PCI</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started prior to PCI</td>
<td>Aspirin 300 mg daily; ticlopidine 250 mg bid for 1 wk followed by 250 mg/d in patients who received stents</td>
<td>IV bolus 5,000 U before PCI followed by IV bolus 70 U/kg to achieve ACT 250–300 s, followed by infusion 10 U/kg/h for 24 h, target APTT 50–70 s</td>
<td></td>
<td>Abciximab: 0/17 Control: 0/14</td>
<td></td>
</tr>
<tr>
<td>ASSENT-3 2001</td>
<td>Symptom onset ≤ 6 h, STE or left BBB</td>
<td>Fibrinolysis, tenecteplase full-dose without abciximab: 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg or half-dose with abciximab (doses ranging from 15–25 mg according to same weight categories as with the full dose)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started prior to fibrinolysis (mean 24 ± 14 min)</td>
<td>Aspirin 150–325 mg/d; ticlopidine or clopidogrel in 30% of patients during hospitalization</td>
<td>In patients not receiving abciximab: IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 1,900 U/h) for 48 h, or eptiopam 30 mg IV bolus, then 1 mg/kg SC q12h for ≤ 7 d, or in patients receiving abciximab: IV bolus 40 U/kg (maximum 3,000 U), followed by an infusion 7 U/kg/h (maximum 800 U/h), adjusted to target APTT 50–70 s</td>
<td></td>
<td>Abciximab: 133/2017 (6.6) Control: 231/4,078 (5.7)</td>
<td>Batches administered before fibrinolysis; initial APTT sample drawn after 3 h</td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Reperfusion Therapy</td>
<td>GP III/IIA Inhibitor Regimen, Dose, Duration Blinded</td>
<td>Routine Antiplatelet Therapy, Dose</td>
<td>UFH Regimen, Dose, Duration</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>Antman et al (ENTIRE-TIMI 23) 2002</td>
<td>Age 21–75 yr; symptom onset ≤ 6 h, STE</td>
<td>Fibrinolysis, tenecteplase full-dose without abciximab: 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg or half-dose with abciximab (doses ranging from 15–25 mg according to same weight categories as with the full dose)</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started ≤ 5 min prior to fibrinolysis</td>
<td>No Aspirin</td>
<td>160 mg po or 230–300 mg IV followed by 100–325 mg/d</td>
<td>30</td>
<td>Abciximab: 8/421 (3.3) Control: 7/242 (2.9)</td>
<td>Boluses administered pre-fibrinolysis; initial APTT sample drawn after 3 h with downward UFH adjustments only in the first 6 h</td>
</tr>
<tr>
<td>GUSTO V 2001</td>
<td>Symptom onset ≤ 6 h, STE or new left BBB</td>
<td>Fibrinolysis, reteplase full-dose without abciximab: 10 × 10^6 U boluses given 30 min apart or half-dose with abciximab</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h</td>
<td>No Aspirin 150–325 mg po or 250–500 mg IV followed by 75–325 mg/d</td>
<td>IV bolus 5,000 U, followed by infusion 1,000 U/h for ≥ 80 kg or 400 U/h for weight &lt; 80 kg, or in patients receiving abciximab: IV bolus 60 U/kg (maximum 5,000 U), followed by an infusion 7 U/kg/h, adjusted to target APTT 1.5–2.5 times control</td>
<td>30</td>
<td>Abciximab: 468/8328 (5.6) Control: 488/8,260 (5.9)</td>
<td></td>
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</tbody>
</table>
As noted above (Section 2.4), the ASSENT-3 study randomized patients \( (n = 6,065) \) within 6 h of STE MI to one of three regimens: full-dose tenecteplase and enoxaparin for up to 7 days \( (n = 2,040) \), half-dose tenecteplase with weight-adjusted low-dose UFH \( (40 \text{ U/kg bolus} \text{[maximum, } 3,000 \text{ U]} \text{ followed by } 7 \text{ U/kg/h} \text{[maximum, } 800 \text{ U/h]} \) to achieve a target APTT from 50 to 70 s) and a 12-h infusion of the GP IIb/IIIa inhibitor abciximab \( (n = 2,017) \); 0.25 mg/kg bolus followed by 0.125 \( \mu \text{g/kg} \text{[maximum, } 10 \mu \text{g/min]} \), or full-dose tenecteplase with weight-adjusted UFH for 48 h \( (n = 2,035) \). The primary, exploratory end points were the composites of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia (efficacy end point), and the above end point plus in-hospital ICH or in-hospital major bleeding complications (efficacy-plus-safety end point). There were significantly fewer efficacy end points in the enoxaparin and abciximab plus low-dose UFH groups than in the standard-dose UFH group: 11.4% and 11.1% vs 15.4% (RR, 0.74; 95% CI, 0.63 to 0.87; \( p = 0.0002 \)); and RR, 0.72; 95% CI, 0.61 to 0.84; \( p < 0.0001 \); respectively). The same was true for the efficacy-plus-safety end point: 13.7% and 14.2% vs 17.0% (RR, 0.81; 95% CI, 0.70 to 0.93; \( p = 0.0037 \)); and RR, 0.84; 95% CI, 0.72 to 0.96; \( p = 0.014 \); respectively). In-hospital reinfarction occurred at lower rates in the enoxaparin and abciximab plus low-dose UFH groups compared with standard-dose UFH \( (2.7% \text{ vs } 2.2% \text{ vs } 4.2%; \text{OR, } 0.0009) \). Rates of stroke \( (1.49% \text{ vs } 1.52%) \) and ICH \( (0.94% \text{ vs } 0.93%) \) were similar in the combination abciximab and low-dose UFH group when compared to the standard-dose UFH group. However, major bleeding (other than ICH; 4.4% vs 2.2%; \( p = 0.0005 \)) and need for transfusions \( (4.2% \text{ vs } 2.3%; \text{p = 0.0032]) \) were significantly higher with combination treatment, with particularly high rates in patients >65 years old \( (7.2% \text{ vs } 3.1%) \). One-year follow-up results demonstrated similar mortality rates among the combination and UFH groups: 9.3% vs 7.9% (RR, 1.18; 95% CI, 0.95 to 1.47; \( p = 0.14 \)); however, 1-year outcome tended to be worse with abciximab and low-dose UFH in a post hoc subgroup analysis of diabetics \( (n = 1,099) \); 17% vs 10%; RR, 1.64; 95% CI, 1.06 to 2.63; \( p = 0.002 \).

Together with the ENTIRE-TIMI 23 phase II study results, a metaanalysis of these three trials \( (n = 23,166) \) [Tables 24, 25] found no difference in those patients receiving abciximab \( (\text{and half-dose fibrinolysis}) \) compared to no abciximab \( (\text{and full-dose fibrinolysis}) \) in 30-day mortality \( (5.8% \text{ vs } 5.8%; \text{OR, } 1.0; 95% \text{ CI, 0.9 to 1.12}; \text{p = 0.95}) \) or 6- to 12-month mortality \( (8.6% \text{ vs } 8.3%; \text{OR, } 1.04; 95% \text{ CI, 0.95 to 1.15}; \text{p = 0.41}) \), despite a reduction in 30-day reinfarction \( (2.3% \text{ vs } 3.6%; \text{OR, } 0.64; 95% \text{ CI, 0.54 to 0.75}; \text{p < 0.001}) \). Major bleeding rates were significantly higher in patients receiving abciximab \( (5.2% \text{ vs } 3.1%; \text{OR, } 1.77; 95% \text{ CI, 1.55 to 2.03}; \text{p < 0.001}) \).

Further, even when using low-dose IV UFH, major bleeding with half-dose fibrinolytic plus abciximab in patients >65 years of age (ASSENT-3) and ICH in patients >75 years of age (GUSTO V) was substantially higher than with standard-dose fibrinolytic and UFH, suggesting that the combination regimen should not be utilized in older patients.

For patients with acute STE MI undergoing PCI, IV GP IIb/IIIa receptor inhibitors have been studied as adjunctive antiplatelet therapy. A metaanalysis of eight randomized trials of eight randomized trials \( (n = 3,949) \) conducted in patients undergoing primary PCI (except for one study with patients after MI undergoing stenting \( [n = 401] \), and another study with patients \( [n = 89] \) undergoing rescue PCI). Abciximab was associated with a significant reduction in 30-day mortality \( (2.4% \text{ vs } 3.4%; \text{OR, } 0.68; 95% \text{ CI, 0.47 to 0.99}; \text{p = 0.047}) \) and 6- to 12-month mortality \( (4.4% \text{ vs } 6.2%; \text{OR, } 0.69; 95% \text{ CI, 0.52 to 0.92}; \text{p = 0.01}) \) [Tables 24, 25]. A significant and direct correlation was demonstrated between the patient’s risk profile and the benefits in 6- to 12-month mortality from abciximab administration as an adjunctive therapy to primary PCI in a metaregression analysis of seven of the randomized trials. Thirty-day reinfarction rates were

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Table 25—GP IIb/IIIa Inhibitor vs Control for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.7)*

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Fibrinolysis</th>
<th>PCI</th>
<th>No. of Deaths†/Patients (%)</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP IIb/IIIa Inhibitor</td>
<td>Control</td>
<td>OR (95% CI)</td>
<td>Events Prevented per 1,000 Treated (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>609/10,586 (5.8)</td>
<td>726/12,580 (5.8)</td>
<td>1.0 (0.9–1.12)</td>
<td>0 (3)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>48/2,016 (2.4)</td>
<td>65/1,933 (3.4)</td>
<td>0.68 (0.47–0.99)</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

*Includes all randomized trials meeting inclusion criteria for the quantitative review by De Luca et al.230
†30 days.
also lower with abciximab compared to control (1.0% vs 1.9%, p = 0.03).230

In the largest trial (n = 2,082) included in the meta-analysis (CADILLAC14), abciximab (administered after the anatomy was defined) was compared to control with either angioplasty or stenting in addition to aspirin (324 mg chewable or 250 mg IV), ticlopidine (500 mg) or clopidogrel (300 mg), and IV UFH (5,000 U bolus); the 6-month composite primary end point of death, reinfarction, disabling stroke, and ischemia-driven revascularization of the target vessel was lowest in patients receiving a stent plus abciximab compared to angioplasty alone, angioplasty plus abciximab, or stenting alone (10.2% vs 20% vs 16.5% vs 11.5%, p < 0.001). However, there were no significant differences among the groups in the rates of death, stroke, or reinfarction; the difference in the incidence of the primary end point was due entirely to differences in the rates of target-vessel revascularization. In contrast, the only double-blind study (ADMIRAL239) found a dramatic reduction in the 30-day composite end point with abciximab compared to placebo (6% vs 14.6%, p = 0.01), in acute STEMI patients (n = 300) also receiving aspirin and IV UFH (70 U/kg bolus; maximum, 7,000 U; with additional boluses administered to achieve an activated clotting time of 200, followed by a continuous infusion of 7 U/kg/h maintained until repeat coronary angiography 24 h after the initial procedure). The greatest benefit in ADMIRAL was seen in the subgroup of patients who received abciximab early (ie, even prior to angiography); 26% of patients were randomly assigned to one of the two study groups in the mobile ICU or emergency department. Again, the main difference between treatment groups was driven by a reduced need for target vessel revascularization. At 3-year follow-up, the primary end point was nonsignificantly lower with abciximab (13.8% vs 21.6%, p = 0.07).240 In contrast to the studies using abciximab in combination with fibrinolysis, the metaanalysis of trials with abciximab compared to control in PCI trials showed similar rates of bleeding (4.7% vs 4.1%; OR; 1.16; 95% CI, 0.83 to 1.59; p = 0.36).

2.8 GP IIb/IIIa Inhibitors

Recommendations

2.8.1 For patients with acute STE MI, we recommend against the combination of standard-dose abciximab and half-dose reteplase or tenecteplase with low-dose IV UFH over standard-dose reteplase or tenecteplase (Grade 1B).

2.8.2 For patients with acute STE MI, we sug-

gest clinicians not use the combination of streptokinase and any GP IIb/IIIa inhibitor (Grade 2B).

2.8.3 For patients with acute STE MI undergoing primary PCI (with or without stenting), we recommend the use of abciximab (Grade 1B). Recommended dosing for abciximab is 0.25 mg/kg IV bolus followed by 0.125 μg/kg/min (maximum, 10 μg/min) for 12 h.

3.0 Facilitated PCI

Facilitated PCI refers to a strategy of planned, immediate PCI after an initial pharmacologic regimen such as half-dose or full-dose fibrinolysis, a GP IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolysis plus a GP IIb/IIIa inhibitor.6 It is important to differentiate facilitated PCI from primary PCI without fibrinolysis or GP IIb/IIIa inhibitor therapy, from primary PCI with a GP IIb/IIIa inhibitor started at the time of PCI, and from rescue PCI after unsuccessful fibrinolysis.

3.1 Fibrinolysis

Six randomized trials,241–246 including two double-blinded, placebo-controlled studies,241,243 were included as part of a quantitative review comparing primary PCI (n = 1,487) compared with facilitated PCI (n = 1,466)247 (Tables 26, 27). Full-dose fibrinolysis (streptokinase,241,244 alteplase,242 tenecteplase245,246) was used in five of the studies, with half-dose lysis (alteplase243) employed in one trial. Aspirin (IV or orally) was administered to all patients; ticlopidine was also used for 1 month in one study,244 even in patients who did not receive a stent. UFH was used in five studies, given as a bolus and infusion for up to 48 h in one study243 (5,000 U followed by 1,000 U/h [or 1,200 U/h for > 80 kg]) but most often as single boluses (eg, 10,000 U with streptokinase and low-dose dextran for 24 h241; 5,000 U of prealteplase followed by additional 5,000-U boluses before and after angiography vs 10,000 U for primary PCI242; 10,000 U for primary PCI244; 60 U/kg [maximum, 4,000 U] with tenecteplase vs 70 U/kg for primary PCI246 with additional boluses to obtain an activated clotting time of 300–350 s in the facilitated PCI group vs 350 to 400 s [250 to 300 s if GP IIb/IIIa inhibitor was used] in the primary PCI group246; the LMWHs fraxiparin (SC for 3 days; in addition to the UFH bolus in the primary PCI group244 and enoxaparin (30 mg IV bolus245) was used in two studies.244 GP IIb/IIIa inhibitors were used in two studies at the time of PCI (facilitated PCI, 23%; vs primary PCI, 87%;245, facilitated PCI, 10%; vs primary PCI, 50%;246).
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration</th>
<th>Heparin Regimen, Dose, Duration</th>
<th>Blinded</th>
<th>Routine Antiplatelet Therapy, Dose</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Zorman et al 235 2002</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started before angiography or after angiography and prior to PCI</td>
<td>UFH IV bolus 70 U/kg</td>
<td>No</td>
<td>Aspirin 250–500 mg</td>
<td>In-hospital</td>
<td>Early abciximab + primary PCI: 0/56 (0) Late abciximab + primary PCI: 4/56 (7.1)</td>
<td>All patients received abciximab before PCI, except third group (n = 51) randomized to no abciximab treatment</td>
</tr>
<tr>
<td>Lee et al (TIGER-PA)252 2003</td>
<td>Symptom onset ≤ 12; STE or LBBB h</td>
<td>Tirofiban 10 μg/kg IV bolus over 3 min, followed by 0.15 μg/kg/min infusion pre-angiography in the emergency department; infusion continued for 24 h</td>
<td>UFH IV bolus 70 U/kg, followed by 5 U/kg/h for early tirofiban administration; IV bolus 100 U/kg, followed by 10 U/kg/h for later tirofiban administration</td>
<td>No</td>
<td>Aspirin, dosing unknown; for stents, clopidogrel 300-mg po loading dose, followed by 75 mg/d or tirofiban 500-mg po loading dose, followed by 250 mg bid for at least 28 d</td>
<td>30</td>
<td>Early tirofiban + primary PCI: 1/50 (2.0) Late tirofiban + primary PCI: 1/50 (2.0)</td>
<td>All patients received tirofiban before PCI</td>
</tr>
<tr>
<td>Mesquita Gabriel et al (ERAMI)250 2003</td>
<td>Symptom onset &lt; 12 h, STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion in the emergency department</td>
<td>UFH IV bolus 5,000 U (77% of patients)</td>
<td>No</td>
<td>Aspirin 250 mg</td>
<td>30</td>
<td>Early abciximab + primary PCI: 0/36 (11.1) Late abciximab + primary PCI: 5/38 (13.2)</td>
<td>All patients received abciximab before PCI</td>
</tr>
<tr>
<td>Arntz et al (REOMOBILE)249 2003</td>
<td>Age &lt; 80 yr; symptom onset &lt; 6 h, STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion pre-angiography in the mobile ICU or before PCI</td>
<td>UFH 70 U/kg IV bolus</td>
<td>No</td>
<td>Aspirin 500 mg</td>
<td>30</td>
<td>Early abciximab + primary PCI: 0/32 (0) Late abciximab + primary PCI: 1/48 (2.1)</td>
<td>All patients received abciximab before PCI</td>
</tr>
<tr>
<td>Cutilip et al 253 2003</td>
<td>Symptom onset ≤ 12 h, STE</td>
<td>Tirofiban 10 μg/kg IV bolus over 3 min, followed by 0.15 μg/kg/min infusion before angiography in the emergency department; infusion continued for 24 h</td>
<td>UFH regimen at the discretion of the treating physician</td>
<td>No</td>
<td>Regimen at the discretion of the treating physician</td>
<td>30</td>
<td>Early tirofiban + primary PCI: 0/28 (0) Late tirofiban + primary PCI: 1/30 (3.3)</td>
<td>All patients received tirofiban before PCI</td>
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<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration</td>
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<tr>
<td>van’t Hof et al (On-TIME)(^{251}) 2004</td>
<td>Age &lt; 80 yr, female age ≥ 50 yr; symptom onset ≤ 6 h; STE</td>
<td>Tirofiban 10 µg/kg IV bolus, followed by 0.15 µg/kg/min infusion before angiography prior to transportation (50%); 2nd bolus after coronary angiography but before PCI; infusion continued for 24 h</td>
<td>UFH IV bolus 5,000 U</td>
<td>Yes</td>
<td>Aspirin 250 mg IV, then unknown dose daily; clopidogrel 300-mg po loading dose, followed by 75 mg/d for 1 mo</td>
<td>30</td>
<td>Early tirofiban + primary PCI: 9/245 (3.7) Late tirofiban + primary PCI: 2/247 (0.8)</td>
<td>All patients received tirofiban before PCI</td>
</tr>
<tr>
<td>Gyongyosi et al (ReoPro-BRIDGING)(^{257}) 2004</td>
<td>Symptom onset ≤ 6 h; STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 µg/kg/min (maximum 10 µg/min) infusion for 12 h started in the emergency department or after coronary angiography and immediately prior to PCI</td>
<td>UFH IV bolus 60 U/kg, followed by an additional bolus to maintain an ACT 200–300 s during the procedure</td>
<td>Yes</td>
<td>Aspirin 250-mg IV bolus, followed by 100 mg/d po; clopidogrel 300-mg oral load, followed by 75 mg/d</td>
<td>30</td>
<td>Early abciximab primary PCI: 0/28 (0) Late abciximab + primary PCI: 0/27 (0)</td>
<td>All patients received abciximab before PCI</td>
</tr>
<tr>
<td>Zeymer et al (INTAMI)(^{254}) 2004</td>
<td>Symptom onset, &lt; 12 h; STE or new left BBB</td>
<td>Eptifibatide 180 µg/kg IV boluses (10 min apart), followed by 2.0 µg/kg/min for &gt; 12–24 h in the emergency department or prior to PCI during PCI (optional)</td>
<td>UFH IV bolus 5,000 U, followed by 1,000 U/h infusion, target APTT 50–70 s</td>
<td>No</td>
<td>Aspirin 50-mg IV bolus, followed by unknown dosing; clopidogrel 300-mg po load, followed by 75 mg/d for ≥ 30 d</td>
<td>30</td>
<td>Early eptifibatide + primary PCI: 2/53 (3.8) Late (or no) eptifibatide + primary PCI: 2/40 (4.1)</td>
<td>4 patients without evidence of acute MI during coronary angiography subsequently excluded from analysis; eptifibatide started after coronary angiography before (n = 30) or during (n = 12) PCI</td>
</tr>
<tr>
<td>Gibson et al (TITAN-TIMI 34)(^{256}) 2006</td>
<td>Symptom onset ≤ 6 h STE</td>
<td>Eptifibatide 180 µg/kg IV boluses (10 min apart), followed by 2.0 µg/kg/min</td>
<td>UFH IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 7 U/kg/h (maximum 800 U/h)</td>
<td>No</td>
<td>Aspirin 160–325 mg/d po</td>
<td>30</td>
<td>Early eptifibatide + primary PCI: 7/180 (4.0) Late eptifibatide + primary PCI: 5/163 (2.8)</td>
<td>All patients received eptifibatide before PCI</td>
</tr>
<tr>
<td>Study Year</td>
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<td>Heparin Regimen, Dose, Duration</td>
<td>Routine Antiplatelet Therapy, Dose, Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>Rakowski et al(^{257}) 2007</td>
<td>Symptom onset ≤ 12 h; STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by 0.125 mg/kg/min infusion for 12 h started in the emergency department or after coronary angiography and immediately prior to PCI</td>
<td>UFH IV bolus 70 U/kg (maximum 7,000 U); additional boluses administered to achieve an ACT of 200 s, followed by an infusion 7 U/kg/h for 24 h post-PCI, target APTT 1.5–2 times control</td>
<td>No</td>
<td>30</td>
<td>Early abciximab primary PCI: 0/25 (0) Late abciximab primary PCI: 0/25 (0)</td>
<td></td>
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</tr>
<tr>
<td>Maioli et al(^{258}) 2007</td>
<td>Symptom onset ≤ 12 h; STE</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 mg/kg/min infusion for 12 h started in the emergency department or after coronary angiography and immediately prior to PCI</td>
<td>UFH IV bolus 70 U/kg, with additional boluses to maintain an ACT of 200–250 s</td>
<td>Aspirin 300–500 mg po, followed by 75 mg/d; clopidogrel 300 mg po, followed by 75 mg/d or ticlopidine 500 mg/d for 30 d</td>
<td>30</td>
<td>Early abciximab primary PCI: 3/105 (2.9) Late abciximab primary PCI: 6/105 (5.7)</td>
<td></td>
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<tr>
<td>ASSENT-4 PCI(^{246}) 2006</td>
<td>Symptom onset ≤ 6 h; STE ≥ 0.1 mV across multiple LEADS</td>
<td>Tenecteplase full-dose: 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for weight ≥ 90 kg.</td>
<td>UFH IV bolus 70 U/kg (maximum), or in patients receiving PCI (with full-dose tenecteplase): UFH IV bolus 80 U/kg (maximum)</td>
<td>Aspirin 150–325 mg; clopidogrel 300-mg po load, followed by 75 mg/d</td>
<td>90</td>
<td>Tenecteplase + PCI: 138/1,535 (9.0) Primary PCI: 117/1,409 (8.4)</td>
<td></td>
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</tbody>
</table>

Includes 55 patients from earlier publication \(^{255}\) reporting myocardial scintigraphic results; all patients received abciximab before PCI.
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration</th>
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<th>Routine Antiplatelet Therapy, Dose</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
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</thead>
<tbody>
<tr>
<td>O’Neill et al241 1992</td>
<td>Age ≤ 76 h; symptom onset ≤ 4 h; STE</td>
<td>Streptokinase 1.5 × 10^6 U IV bolus followed by 5,000 U IV bolus at the initiation of the angioplasty, then continuous infusion for 24 h to maintain an ACT ≥ 180 s interrupted by sheath removal, then restarted for an additional 3–5 d</td>
<td>UFH 10,000 U IV bolus followed by 5,000 U IV bolus</td>
<td>Yes</td>
<td>Aspirin 325 mg po</td>
<td>In-hospital</td>
<td>Streptokinase + PCI: 0/58 (0) Primary PCI: 0/63 (0)</td>
<td></td>
</tr>
<tr>
<td>Widimsky et al (PRAGUE)244 2000</td>
<td>Symptom onset &lt; 6 h; STE or left BBB</td>
<td>Streptokinase 1.5 × 10^6 U over 1 h</td>
<td>UFH 5,000 U IV bolus in primary PCI group only; all patients received fraxiparin for 3 d post-MI</td>
<td>No</td>
<td>Aspirin 900 mg IV; ticlopidine 500 mg/d</td>
<td>30</td>
<td>Streptokinase + PCI: 12/100 (12) Primary PCI: 7/101 (6.9) Excluding 99 patients who had fibrinolysis alone (third treatment group)</td>
<td></td>
</tr>
<tr>
<td>Vermeer et al242 1999</td>
<td>Age &lt; 80 yr; symptom onset &lt; 6 h; STE or ST-segment depression ≥ 1.5 mV in ≥ 1 lead</td>
<td>tPA bolus over 90 min (15-mg bolus + 0.75 mg/kg [maximum 50 mg] over 30 min + 0.5 mg/kg [maximum 35 mg] over 60 min)</td>
<td>UFH 5,000 U IV bolus before tPA or 1,000 U IV bolus before primary PCI; 2nd 5,000 U IV bolus given at the start of the coronary angiogram; 3rd 5,000 U IV bolus given post-PCI; followed by IV infusion, target APTT 2–3 times normal</td>
<td>No</td>
<td>Aspirin 300 mg IV or 160 mg po, followed by 80 mg/d</td>
<td>42</td>
<td>tPA + PCI: 6/74 (8.1) Primary PCI: 5/75 (6.7) Excluding 75 patients who had fibrinolysis alone (third treatment group)</td>
<td></td>
</tr>
<tr>
<td>Ross et al (PACT)243 1999</td>
<td>Age ≤ 75 yr; symptom onset ≤ 6 h; STE</td>
<td>tPA 50 mg over 3 min</td>
<td>UFH 5,000 U IV bolus, followed by an infusion of 1,000 U/h (or 1,200 U/h for patients &gt; 80 kg) for 48 h, target APTT 60–85 s</td>
<td>Yes</td>
<td>Aspirin daily, dose unknown</td>
<td>30</td>
<td>tPA + PCI: 11/302 (3.6) Primary PCI: 10/304 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration</td>
<td>Heparin Regimen, Dose, Duration</td>
<td>Blinded</td>
<td>Routine Antiplatelet Therapy, Dose</td>
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<tr>
<td>Fernandez-Aviles et al (GRACIA-2) 2004</td>
<td>Symptom onset ≤ 12 h; STE</td>
<td>Tenecteplase full-dose: 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg; abciximab 0.25 mg/kg IV bolus, followed by a 0.125 µg/kg/min infusion for 12 h in patients (23%) who received tenecteplase but had TIMI flow grade 0–1 pre-stenting or for patients (87%) undergoing primary PCI</td>
<td>Enoxaparin 30-mg IV bolus for patients receiving tenecteplase</td>
<td>No</td>
<td>Aspirin dosing regimen unknown</td>
<td>30</td>
<td>Tenecteplase + enoxaparin + PCI: 3/104 (2.9)</td>
<td>Abciximab + primary PCI: 5/108 (4.6)</td>
</tr>
<tr>
<td>Le May et al (CAPITAL AMI) 2005</td>
<td>Symptom onset ≤ 6 h; STE or LBBB and anterior (≥ 0.2 mV in ≥ 2 leads), non-anterior (≥ 8 leads with ≥ 0.1 mV STE or ST-segment depression or both, or sum ≥ 2.0 mV), Killip class 3, or systolic BP &lt; 100 mm Hg</td>
<td>Tenecteplase full-dose: 30 mg for weight &lt; 60 kg, 35 mg for weight 60–69.9 kg, 40 mg for weight 70–79.9 kg, 45 mg for weight 80–89.9 kg, and 50 mg for ≥ 90 kg</td>
<td>IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 1,000 U/h) for 48 h, adjusted to target APTT 50–70 s</td>
<td>No</td>
<td>Aspirin 160 mg chewed, followed by 325 mg/d; clopidogrel 300-mg po load, followed by 75 mg/d</td>
<td>30</td>
<td>Tenecteplase: 3/84 (3.6)</td>
<td>Tenecteplase + PCI: 2/86 (2.3)</td>
</tr>
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</table>
Table 26—Continued

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration</th>
<th>Heparin Regimen, Dose, Duration Blinded</th>
<th>Routine Antiplatelet Therapy, Dose</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
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<tbody>
<tr>
<td>ADVANCE MI&lt;sup&gt;260&lt;/sup&gt; 2005</td>
<td>Symptom onset ≤ 6 h; STE or new left BBB</td>
<td>Eptifibatide 180 µg/kg IV boluses (10 min apart), followed by 2.0 µg/kg/min; tenecteplase 0.25 mg/kg IV bolus</td>
<td>IV bolus 40 U/kg (maximum 3,000 U), followed by infusion 7 U/kg/h (maximum 800 U/h) or enoxaparin 0.4 mg/kg IV bolus (maximum 40 mg)</td>
<td>Yes</td>
<td>Aspirin 162–325 mg po; clopidogrel for stenting</td>
<td>30</td>
<td>Tenecteplase + eptifibatide + PCI: 5/74 (6.8) Eptifibatide + primary PCI: 0/77 (0)</td>
</tr>
<tr>
<td>Kastrati et al. (BRAVE)&lt;sup&gt;285&lt;/sup&gt; 2004</td>
<td>Symptom onset &lt; 12 h; STE or new left BBB</td>
<td>Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 µg/kg/min (maximum 10 µg/min) infusion for 12 h; reteplase 5 U IV boluses 30 min apart</td>
<td>UFH 60 U/kg (maximum 5,000 U) IV bolus</td>
<td>No</td>
<td>Aspirin 500 mg IV, followed by 100 mg/d po; clopidogrel 75 mg/d for ≥ 6 mo</td>
<td>30</td>
<td>Reteplase + abciximab + PCI: 2/125 (1.6) Abciximab + primary PCI: 2/128 (1.6)</td>
</tr>
</tbody>
</table>

For patients ≥ 75 yr old, reduced dosing: eptifibatide 2nd bolus omitted and infusion 1.0 µg/kg/min infusion; tenecteplase 0.20 mg/kg; UFH bolus 30 U/kg (maximum 2,000 U), followed by infusion 4 U/kg/h (maximum 400 U/h); enoxaparin bolus 0.3 mg/kg (maximum 30 mg); intention-to-treat analysis: 74 patients originally randomized to each treatment group; however, no eptifibatide given to 1 patient in each group and 4 patients assigned to tenecteplase did not receive this therapy.
Despite significantly better initial pre-PCI and post-PCI rates of TIMI flow grade 3 in two trials, overall mortality was significantly increased in the facilitated compared with the primary PCI group (5.6% vs 4.0%; OR, 1.43; 95% CI, 1.01 to 2.02; p = 0.042). Reinfarction (4.4% vs 2.4%; OR, 1.81; 95% CI, 1.19 to 2.77; p = 0.006) and short-term target vessel revascularization (4.8% vs 1.0%; OR, 4.81; 95% CI, 2.47 to 9.37; p < 0.0001) were also significantly higher in the facilitated group. Even after excluding the largest trial (n = 1,657), target vessel revascularization rates remained higher in the facilitated compared to the primary PCI group (6.4% vs 1.2%; OR, 5.08; 95% CI, 1.35 to 19.1; p = 0.016).ICH (1.0% vs 0.1%, p = 0.0007) and total stroke (1.6% vs 0.3%, p = 0.0002) were significantly higher in the facilitated group; major bleeding also tended to be higher (6.5% vs 4.5%, p = 0.17).

The ASSENT-4 PCI study contributed > 50% of the patients included in the quantitative review of randomized trials. The study randomized patients with STE MI within 6 h of symptom onset scheduled to undergo primary PCI but with an anticipated delay of 1 to 3 h to primary PCI (n = 838) or PCI preceded by full-dose tenecteplase (n = 829). Of the patients enrolled, 20% were first treated in ambulances, 35% in hospitals without catheterization facilities, and 45% in hospitals with catheterization facilities; it is important to note that, while almost half of the patients were randomized in primary PCI-capable centers, the time from randomization to first balloon in both groups was still well beyond the guideline-recommended 90-min maximum delay at a median of 115 min in the facilitated PCI group and 107 min in the primary PCI group. In addition, patients were required to have total STEs ≥ 0.6 mV across multiple leads or, for inferior MI, ST deviations ≥ 0.6 mV provided STEs ≥ 0.4 mV were present in the inferior leads; or new left BBB with concordant STE ≥ 0.1 mV. All patients received aspirin and an IV bolus of UFH (70 U/kg in the primary PCI group and 60 U/kg [maximum, 4,000 U] in the facilitated PCI group). Use of GP IIb/IIIa inhibitors was left to the discretion of the treating physician in primary PCI patients (and were used in 50%); however, in the facilitated PCI group, GP IIb/IIIa inhibitors could only be used in bailout situations (e.g., large residual clot with no, or suboptimal, recanalization of the IRA; used in 10% of patients). Early cessation of enrollment was recommended by the data and safety monitoring board because of higher in-hospital mortality in the facilitated compared to the primary PCI group (6% vs 3%, p = 0.01). While the 3% absolute difference in mortality led to the discontinuation of ASSENT-4 PCI well short of the target sample size, the difference in the absolute number of deaths was small (43/664 vs 22/656). The primary end point (death, congestive heart failure, or shock within 90 days of randomization) was also significantly higher in the facilitated group (19% vs 13%; RR, 1.39; 95% CI, 1.11 to 1.74; p = 0.0045). Reinfarction (6% vs 4%, p = 0.03) and repeat target vessel revascularization (7% vs 3%, p = 0.004) were higher in the facilitated group. In-hospital stroke was also significantly higher (1.8% vs 0%, p < 0.0001) in the facilitated group, but noncerebral bleeding complications were similar (6% vs 4%, p = 0.3). It is important to note that the death rate in the primary PCI group was unusually low, whereas the rate in the facilitated PCI group was consistent with that observed in patients receiving tenecteplase alone compared with previous trials. Further, patients in the facilitated group received full-dose tenecteplase and a single IV bolus of UFH without an infusion despite a median 104 min delay to first balloon (at which time they could receive addi-
tional IV boluses); this may have exposed those patients with successful reperfusion after tenecteplase in the facilitated group to IRA reocclusion since suboptimal anticoagulation may have been present with a single IV bolus of UFH. Nevertheless, a strategy of routine PCI preceded by full-dose fibrinolysis with antithrombotic cotherapy as used in ASSENT-4 PCI cannot be recommended and could be harmful.

Another study248 not included in the quantitative review247 randomized patients (n = 170) with high-risk (STE or LBBB plus additional ECG or hemodynamic criteria) to treatment with tenecteplase alone or full-dose tenecteplase followed by PCI. The primary endpoint of 6-month death, reinfarction, recurrent unstable ischemia, or stroke was significantly lower in the facilitated PCI group compared to fibrinolysis alone (11.6% vs 24.4%, p = 0.04). Reinfarction tended to be lower with facilitated PCI (5.8% vs 14.6%, p = 0.07); no differences in major bleeding were observed (8.1% vs 7.1%, p = 1.0).

3.2 GP IIb/IIIa Inhibitors

Nine randomized trials,217,235,249–255 including one double-blinded, placebo-controlled study,251 were included as part of a quantitative review comparing primary PCI (n = 573) with facilitated PCI (n = 575) PCI.247 Abciximab was used in five studies,217,235,249,250,255 tirofiban in three studies,251–253 and eptifibatide in one study.254 (Tables 26, 27).

Initial rates of TIMI grade 3 flow were significantly higher in studies217,235,249,250,253–255 with facilitated PCI using GP IIb/IIIa inhibitors than in those with primary PCI (31% vs 19%; OR, 2.6; 95% CI, 1.36 to 4.95; p = 0.004); final rates tended to be higher with facilitated PCI (55% vs 53%; OR, 1.79; 95% CI, 0.93 to 3.44; p = 0.05). However, mortality (3.0% vs 3.0%; OR, 1.03; 95% CI, 0.49 to 2.17; p = 0.94), reinfarction (1.5% vs 0.7%; OR, 1.40; 95% CI, 0.49 to 3.98; p = 0.53), and short-term urgent target vessel revascularization (2.0% vs 1.7%, p = 0.99) were similar in the facilitated and primary PCI groups.251 ICH (0% vs 0.2%, p = 0.68), total stroke (0% vs 0.4%, p = 0.34), and major bleeding (7% vs 5%, p = 0.30) rates were similar in the two groups.

Further data not included in the above-mentioned review includes two additional studies256,257 and final data in a larger sample of patients258 from another study previously published.255 A pilot study256 of eptifibatide in the emergency department in patients (n = 180) with STE MI presenting within 6 h of symptom onset and undergoing primary PCI demonstrated improved angiographic perfusion (TIMI frame count) prior to PCI compared to eptifibatide after diagnostic angiography in the catheterization laboratory (n = 163), without an increase in bleeding risk. Similarly, abciximab in the emergency department in patients with a first or anterior STE MI resulted in better angiographic and myocardial perfusion (assessed by scintigraphic253 and STE resolution257,258) and left ventricular function.

3.3 Combination Reduced-Dose Fibrinolysis and GP IIb/IIIa Inhibitors

Two randomized trials,259,260 including one double-blind, placebo-controlled study,260 were included as part of a quantitative review comparing primary PCI (n = 205) with facilitated PCI (n = 194) PCI.247 (Tables 26, 27). Half-dose fibrinolysis (reteplase259 or tenecteplase250) with a standard dose of GP IIb/IIIa inhibitor (abciximab259 or eptifibatide) was compared with standard doses of GP IIb/IIIa inhibitor prior to primary PCI. All patients received aspirin (500 mg IV259 or 162 to 325 mg po260) and IV UFH (60 U/kg [maximum dose, 5,000 U]259 or 40 U/kg bolus [maximum, 3,000 U]) with 7 U/kg/h [maximum, 800 U/h260] or IV enoxaparin (0.4 mg/kg bolus [maximum, 40 mg]).260

The primary end point in one trial259 was infarct size, and this was not reduced with the facilitated combination compared with abciximab alone. The other trial was prematurely terminated (n = 148 of a planned 5,640) as a result of slow recruitment260 despite improved IUA patency (TIMI flow grades 2 or 3), there was a higher rate of the primary end point (death or new/worsening severe heart failure at 30 days) in the half-dose tenecteplase plus eptifibatide compared to the eptifibatide-only group (11% vs 1%, p = 0.02). In addition, major bleeding rates were significantly higher in the facilitated combination group (TIMI major bleeding 23% vs 7%; p = 0.05; GUSTO moderate-to-severe bleeding 24% vs 9%, p = 0.02). Combining these two trials,247 there was no different in mortality, reinfarction, or urgent target vessel revascularization. ICH (0.9% vs 0.1%, p = 0.0004) and major bleeding (12% vs 5%, p = 0.006) were significantly higher in the facilitated combination group.

The Facilitated Intervention With Enhanced Reperfusion Speed To Stop Events study261 is a recently published prospective, multicenter, randomized, double-blind, placebo-controlled trial of STE MI or new left BBB patients (n = 3,000) presenting within 6 h of symptom onset undergoing PCI when the door-to-balloon time is from 1 and 4 h after hospital presentation. The study was designed to compare the efficacy and safety of early administration of the following: (1) reduced-dose reteplase and standard-dose abciximab combination therapy, (2) abciximab alone.
followed by primary PCI, or (3) abciximab alone administered just before PCI. All patients will receive aspirin (81 to 325 mg po or 250 to 500 mg IV) and either IV UFH (40 U/kg [maximum, 3,000 U] bolus with additional UFH given in the catheterization laboratory to achieve an ACT time of 200 to 250 s) or IV enoxaparin (0.5 mg/kg IV plus simultaneous 0.3 m/kg SC). The primary efficacy end point of Facilitated Intervention With Enhanced Reperfusion Speed To Stop Events (or FINESSE) was the composite of all-cause mortality or post-MI complications (resuscitated ventricular fibrillation occurring >48 h after randomization, rehospitalization or emergency department visit for congestive heart failure, or cardiogenic shock within 90 days of randomization). The results have now just been published,271 and, while not formally included in this review, the results are consistent with previous data showing no improvement in outcomes with facilitation of PCI with fibrinolysis plus abciximab compared with abciximab given at the time of primary PCI.

3.0 FACILITATED PCI

Recommendations

3.0.1 For patients with acute STE MI undergoing primary PCI, we recommend against the use of fibrinolysis, with or without a GP IIb/IIIa inhibitor (Grade 1B).

3.0.2 For patients with acute STE MI who are to undergo primary PCI, we suggest administration of a GP IIb/IIIa inhibitor prior to coronary angiography (Grade 2B). The largest number of patients studied in this setting received abciximab, 0.25 mg/kg IV bolus, followed by 0.125 μg/kg/min (maximum 10 μg/min) for 12 h; recommended dosing for eptifibatide is two 180-μg IV boluses (10 min apart) followed by 2.0 μg/kg/min infusion for 12 to 24 h; recommended dosing for tirofiban is 25 μg/kg IV bolus followed by 0.15 μg/kg/min for 24 h.

4.0 RESCUE PCI

Rescue (also known as salvage) PCI is defined as PCI within 12 h after failed fibrinolysis for patients with continuing or recurrent myocardial ischemia.6 Five randomized trials242,262-265 have compared rescue PCI to a conservative approach after failed fibrinolysis in patients (n = 920) with STE MI (Tables 28, 29), and were included in a metaanalysis.266 Rescue PCI was performed within 12 h of symptom onset in all trials. In the first two trials,262,263 randomization took place after angiography revealed IRA occlusion; in one trial242 randomization occurred before angiography but the decision to proceed to rescue PCI was based on an occluded IRA. In the two more recent trials, patients were randomized 60 min after fibrinolysis if the lead with maximal STE pretreatment had failed to resolve by 50% and in the absence of an accelerated idioventricular rhythm by the time of the 60-min ECG,264 or 90 ± 15 min after fibrinolysis if there was a <50% resolution of the ST-segment in the lead with maximal STE pretreatment.265 In these two trials,264,265 the use of stents (50.3%264 and 68.5%,265 respectively) and GP IIb/IIIa inhibitors (3.3%264 and 43.4%,265 respectively) at the time of rescue PCI was left to the discretion of the treating physician.

Mortality tended to be lower with rescue PCI compared to conservative therapy (6.9% vs 10.7%; OR, 0.63; 95% CI, 0.39 to 1.01; p = 0.055) within the first 30 days of follow-up.266 At longer-term follow-up (up to 1 year), there remained a numerically but nonsignificantly lower rate of death in the rescue PCI group (8.9% vs 12.0%; OR, 0.69; 95% CI, 0.41 to 1.57; p = 0.16). There was also a reduction of the combined end point of death or reinfarction in favor of rescue PCI at both short-term (10.8% vs 16.8%; OR, 0.60; 95% CI, 0.41 to 0.89; p = 0.012) and longer-term (OR, 0.60; 95% CI, 0.39 to 0.92; p = 0.019) follow-up. Rescue PCI was associated with substantially and significantly more major bleeding (11.9% vs 1.3%; OR, 9.05; 95% CI, 3.71 to 22.06; p < 0.001), mainly (82% of cases) associated with the femoral sheath used for catheterization, and none were fatal; of note, 69% of these rescue PCI patients with major bleeding had received GP IIb/IIIa inhibitor (abciximab) compared with 43% overall.

The Middlesbrough Early Revascularization To Limit Infarction trial,264 a single-center study, found no difference in the primary end point of 30-day mortality between the rescue and conservative groups (9.8% vs 11%; absolute difference, 1.2%; 95% CI, −5.8% to 8.3%; p = 0.7); however, the study was powered to detect an unrealistic and extremely large 12% absolute mortality difference. The secondary end point of death, reinfarction, stroke, subsequent revascularization, and heart failure occurred less frequently in the rescue group (37.3% vs 50%; absolute difference, 12.7%; 95% CI, 1.6 to 23.5%; p = 0.02), driven by less subsequent revascularization (6.5% vs 20.1%; absolute difference, 13.6%; 95% CI, 6.2 to 21.4%; p < 0.01). However, strokes (4.6% vs 0.6%, p = 0.03) and transfusions (11.1% vs 1.3%, p < 0.001) were more common in the
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient and ECG Features</th>
<th>Fibrinolytic Therapy</th>
<th>Determination of Failure of Fibrinolysis</th>
<th>Antiplatelet Therapy</th>
<th>Antithrombin Therapy</th>
<th>Time to Angiography/PCI, min</th>
<th>Duration of Follow-up, d</th>
<th>Mortality, No./Total (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belenkie et al 1992</td>
<td>Age &lt; 76 yr; symptom onset ≤ 3 h; STE</td>
<td>Streptokinase tPA</td>
<td>Angiography undertaken immediately after initiation of fibrinolysis; patients with occluded IRA &gt; 3 h after symptom onset</td>
<td>Aspirin 325 mg</td>
<td>IV UFH 5,000 U bolus, followed by infusion to maintain APTT 1.5–2.5 times control until discharge</td>
<td>Unknown</td>
<td>In-hospital</td>
<td>1/16 (6.3)</td>
<td>Rescue PCI: 1/16 (6.3) Conservative: 4/12 (33.3)</td>
</tr>
<tr>
<td>Ellis et al (RESCUE) 1994</td>
<td>Age &lt; 80 yr; coronary angiography ≤ 6 h of symptom onset or ≤ 8 h if severe ongoing chest pain; anterior STE MI</td>
<td>Streptokinase tPA; urokinase; for patients randomized to PCI who had received fibrin-specific agent (tPA), additional streptokinase (500,000 U) or urokinase (1 x 10^6 U) administered; tPA</td>
<td>TIMI flow grade 0–1 in the LAD after IC nitrate administration and ≥ 90 min post-initiation of fibrinolysis</td>
<td>Aspirin 325 mg chewed, followed by 80–325 mg/d</td>
<td>IV or SC (&gt; 10,000 U bid) UFH for ≥ 3 d</td>
<td>Unknown</td>
<td>30</td>
<td>4/78 (5.1) Rescue PCI: 4/78 (5.1) Conservative: 7/73 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Vermeer et al 1999</td>
<td>Age &lt; 80 yr; symptom onset &lt; 6 h; STE or ST-segment depression ≥ 1.5 mV in ≥ 1 lead</td>
<td>TIMI 0–1 flow at the angiogram performed 60–120 min post-lytic administration</td>
<td>Aspirin 300 mg IV or 160 mg po, followed by 80 mg/d po</td>
<td>IV UFH 5,000-U bolus, followed by an additional 5,000-U bolus at the start of the coronary angiogram, followed by an additional 5,000-U bolus after completion of the PCI, followed by an infusion, titrated to an APTT 2–3 times control for 24 h</td>
<td>From symptom onset to angiography: 240</td>
<td>42</td>
<td>Rescue PCI: 6/74 (8.1) Conservative: 5/75 (6.7)</td>
<td>Excluding 75 patients who primary PCI (third treatment group)</td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Patient and ECG Features</td>
<td>Fibrinolytic Therapy</td>
<td>Determination of Failure of Fibrinolysis</td>
<td>Antiplatelet Therapy</td>
<td>Antithrombin Therapy</td>
<td>Time to Angiography/PCI, min</td>
<td>Duration of Follow-up, d</td>
<td>Mortality, No./Total (%)</td>
<td>Comments</td>
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<tr>
<td>Sutton et al (MERLIN)(^{26}) 2004</td>
<td>Symptom onset ≤ 10 h; STE</td>
<td>Streptokinase (n = 296; 96%); tPA (n = 11; 4%)</td>
<td>2nd 12-lead ECG obtained 60 min after onset of fibrinolysis showing failure of STE (in lead with maximal STE at baseline) to have resolved by 50% and absence of an AIVR</td>
<td>Aspirin 300 mg, followed by 75 mg/d; other antiplatelet therapies (e.g., thienopyridines and GP IIb/IIIa inhibitors) at discretion of treating MD; clopidogrel (300 mg, followed by 75 mg/d) or ticlopidine (500 mg, followed by 250 mg bid) after stent</td>
<td>IV UFH for all patients undergoing PCI, target ACT 300 s</td>
<td>From symptom onset to angiography: 327 ± 121; from 60-min ECG to angiography: 85 ± 36</td>
<td>30</td>
<td>Rescue PCI: 15/153 (9.8)</td>
<td>Conservative: 17/154 (11.0)</td>
</tr>
<tr>
<td>Gershlick et al (REACT)(^{25}) 2005</td>
<td>Age ≤ 85 yr;</td>
<td>Streptokinase (n = 254; 60%); reteplase (n = 113; 27%); tPA (n = 50; 12%); tenecteplase (n = 10; 2%); repeat fibrinolysis group received a fibrin-specific lytic (tPA or reteplase) according to physician choice</td>
<td>12-lead ECG obtained 90 ± 15 min after onset of fibrinolysis showing failure of STE (in lead with maximal STE at baseline) to have resolved by 50%, with or without chest pain</td>
<td>Aspirin dosing unknown; GP IIb/IIIa inhibitors at discretion of treating MD</td>
<td>IV UFH according to standard practice; in repeat fibrinolysis and conservative groups, titrated to APTT 1.5–2.5 times control; no LMWH in the first 24 h</td>
<td>From symptom onset to PCI: 414 (25–75 percentiles, 350–505); from fibrinolysis to PCI: 276</td>
<td>180</td>
<td>Rescue PCI: 9/144 (6.2)</td>
<td>Conservative: 18/141 (12.8)</td>
</tr>
</tbody>
</table>

* LAD = left anterior descending; IC = intracoronary; AIVR = accelerated idioventricular rhythm.
Table 29—Randomized Trials of Rescue PCI vs Conservative Care or Repeat Fibrinolysis in Acute STE MI: Summary Evidence Profile (Section 4.0)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>No. of Deaths*/Patients (%)</th>
<th>Rescue PCI Alternative Care OR (95% CI)</th>
<th>Events Prevented per 1,000 Treated, No. (SD)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative care = conservative care</td>
<td>Rescue PCI Alternative Care Alternative Care OR (95% CI)</td>
<td>Events Prevented per 1,000 Treated, No. (SD)</td>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>3†</td>
<td>10/160 (6.3)</td>
<td>17/168 (10.1)</td>
<td>0.59 (0.26–1.34)</td>
<td>39 (30)</td>
</tr>
<tr>
<td>2‡</td>
<td>22/294 (7.5)</td>
<td>32/298 (10.7)</td>
<td>0.67 (0.38–1.19)</td>
<td>33 (24)</td>
</tr>
<tr>
<td>5§</td>
<td>32/462 (6.9)</td>
<td>49/462 (10.6)</td>
<td>0.63 (0.39–1.00)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>Alternative care = repeat fibrinolysis</td>
<td>1</td>
<td>9/144 (6.2)</td>
<td>18/142 (12.7)</td>
<td>0.46 (0.20–1.06)</td>
</tr>
</tbody>
</table>

*Up to 180 days.†Trials where rescue PCI vs conservative care performed after coronary angiography demonstrated occluded IRA.‡Trials where rescue PCI vs conservative care performed based on lack of STE resolution and before coronary angiography.§All trials comparing rescue PCI vs conservative care.

rescue group; these findings must be placed in the context of the use of repeated fibrinolysis in 11.7% of the conservatively treated patients. One-year follow-up again showed similar mortality rates in the rescue and conservative groups (13% vs 14.4%; absolute difference, 1.4%; 95% CI, −6.4 to 9.3%; p = 0.7). The composite secondary end point remained lower in the rescue group (43.1% vs 57.8%, p = 0.01), again driven mainly by less subsequent revascularization (12.4% vs 29.9%, p < 0.001). A trend toward higher stroke rates in the rescue group was observed (5.2% vs 1.3%, p = 0.06).

The Rescue Angioplasty vs Conservative Treatment or Repeat Thrombolysis trial was multicenter and included 19 of 35 hospitals with on-site angiographic facilities. Importantly, the median time from presentation until fibrinolytic treatment (door-to-needle time) was 27 min (interquartile range, 16 to 43 min). In addition to the randomized treatment groups of rescue PCI (n = 144) and conservative therapy (n = 141), another group (n = 142) was assigned to repeated fibrinolysis with a fibrin-specific lytic; streptokinase was used initially in 57.7% of this group. Of the patients randomized to rescue PCI, 61% were enrolled at hospitals with interventional capabilities; the median transfer time for patients from hospitals without interventional capabilities was a median of 85 min (interquartile range, 55 to 120 min). Patients receiving conservative therapy or repeat fibrinolysis received IV UFH for 24 h to a target APTT of 1.5 to 2.5. The composite primary end point of death, reinfarction, stroke, or severe heart failure within 6 months was significantly lower among patients treated with rescue PCI as compared to either those receiving conservative therapy or those undergoing repeat fibrinolysis (15.3% vs 29.8% vs 31.0%, p < 0.01; adjusted pairwise comparison between rescue PCI and conservative therapy: HR, 0.47; 95% CI, 0.28 to 0.79; p = 0.004; and between rescue PCI and repeated fibrinolysis: HR, 0.43; 95% CI, 0.26 to 0.72; p = 0.001). Among patients assigned to rescue PCI, there was no significant difference in event rates between those who were transferred for intervention and those who were recruited in hospitals with on-site facilities for intervention (16.4% vs 14.6%, p = 0.8). Death from any cause was numerically, but not significantly, lower in the rescue PCI group (6.2% vs 12.8% vs 12.7%, p = 0.12); recurrent MI was significantly lower in the rescue PCI group (2.1% vs 8.5% vs 10.6%, p < 0.01). There were no significant differences among the groups in major bleeding events; however, there was a tendency toward higher mortality from major bleeding episodes in the repeated fibrinolysis group (four deaths from hemopericardium, and one death from ICH) and the conservative therapy group (one death from hemothorax and two deaths from ICH) than in the rescue PCI group (no deaths associated with bleeding events).

4.0 Rescue PCI

Recommendation

4.0.1 For patients with STE MI who have received fibrinolysis but have persistent STE (< 50% resolution 90 min after treatment initiation compared with the pretreatment ECG), we recommend rescue PCI should be performed over repeat fibrinolysis or no additional reperfusion therapy (Grade 1B), and suggest as soon as possible and within 2 h of identification of lack of STE resolution (Grade 2C).

Conflict of Interest Disclosures

Dr. Goodman discloses that he has received grant monies from Biovail, Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-La Roche, Lilly, Merek, Sanofi-Aventis, Schering, and The Medicines Company. He has also received consultant fees from...
Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-La Roche, Lilly, Sanofi-Aventis, and The Medicines Company.

Dr. Menon discloses that he is on the speakers bureau for Roche and Datascope, and that he has served on an advisory committee for Roche.

Dr. Cannon discloses that he has received grant monies from Accumetics, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Sanofi-Aventis, and Schering Plough.

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REFERENCES

5 Williams DO. Treatment delayed is treatment denied. Circulation 2004; 109:1806–1808
8 PCTA Collaborators. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow-up and analysis of individual patient data from randomized trials. Am Heart J 2003; 145:47–57
18 Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? Am J Cardiol 2003; 92:824–826
34 LATE Study Group. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. Lancet 1993; 342:759–766
36 The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. Lancet 1990; 336:71–75
42 Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group.
Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity from all randomised trials of more than 1000 patients. Lancet 1994; 343:311–322


Thiemann DR, Coresh J, Schulman SP, et al. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 2000; 101:2239–2246


Rawles J. Halving of mortality at 1 year by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). J Am Coll Cardiol 1994; 23:1–5


76 Sloan MA, Guigliano RP, Thompson SL. Prediction of intracranial hemorrhage in the InTIME-II trial. 2001; 372A


100 The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, left ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615–1622


168 The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized


factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction: the PENTALYSE study. Eur Heart J 2001; 22:1716–1724


229 Lincoff AM, Calif RM, Van de Werf F, et al. Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs. conventional fibrinolytic therapy for acute myocardial infarction: GUSTO V randomized trial. JAMA 2002; 288:2130–2135


260 The ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated Addressing the Value of Facilitated Angioplasty after Combination Therapy or Epifibatide Monotherapy in Acute Myocardial Infarction (ADVANCE MI) trial. Am Heart J 2005; 150:116–122


