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Acute ST-Segment Elevation Myocardial Infarction*

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

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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. ***(CHEST 2008; 133:708S–775S)***

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 (*eg*, tenecteplase) to facilitate the ease of administration and potentially reduce the risk of non-intracranial hemorrhage (ICH)-related bleeding (tenecteplase) [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,

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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

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

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)**.**

Acute 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 recommendation in the STE MI chapter are based on the potential for mortality reduction (benefit) vs bleeding (risk), with relatively less emphasis placed on the reduction in reinfarction, the composite of death, MI, or stroke, or other clinically important outcomes (*eg*, recurrent ischemia).

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 overview[9] 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 analysis[18] 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 study[19] found that primary PCI was associated with signif-

Table 1—*Question Definition and Eligibility Criteria (Section: Intro)

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

*RCT = randomized controlled trial; CHF = congestive heart failure.

icantly 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[20] and optimal[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.[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,[24] and it has been suggested that PCI be considered for achieving reperfusion in these patients.[23,25,26]

1.0 Reperfusion Therapy

Recommendation

1.0.1. 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 PCI or fibrinolytic) therapy and have a reperfusion strategy implemented promptly after contact with the health-care system (Grade 1A).

1.1 Fibrinolysis

More than 150,000 patients have been randomized in trials of fibrinolytics vs placebo/control, or one fibrinolytic regiment 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) analysis[42]—a collaborative overview of early mortality and major morbidity results from nine trials[27–34] 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 < 180 mm Hg systolic),[43,44] 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 analyses[45,46] questioned the benefit of fibrinolytic therapy in the elderly, with one of these studies[45] 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 study[48] 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 trials[49–54] 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 trial[56]) 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 minh 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).[59] Similarly, patients in the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis trial[60] 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 registry[55] 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)***

Study Year	Entry ECG Features %	Time From Symptom Onset to Randomization, h (%)	Fibrinolytic Regimen	Control	Routine Antiplatelet	Routine Heparin, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total Patients (%); RR (95% CI)	Comments
GISSI-1[27] 1984–1985	STE 91 BBB 1 ST-segment depression 4 Other 5 Normal 0	0–6 (83); 7–12 (17)	Streptokinase 1.5 × 10^6 U over 1 h	Open	No	No	35	Streptokinase: 628/5,860 (10.7) Control: 758/5,852 (13.0); 0.81 (0.72–0.90)	
ISAM[28] 1982–1985	STE 94 BBB 5 ST-segment depression 0 Other 1 Normal 0	0–6 (100)	Streptokinase 1.5 × 10^6 U over 1 h	Placebo	Aspirin (single IV bolus)	Yes, IV 5,000 U + 800–1,000 U/h for 72–96 h, then oral anticoagulant	21	Streptokinase: 54/859 (6.3) Placebo: 63/882 (7.1); 0.88	
AIMS[29] 1985–1987	STE 99 BBB 0 ST-segment depression 1 Other 0 Normal 0	0–6 (100)	APSAC 30 U over 5 min	Placebo	No	Yes, IV 1,000–1,500 U/h starting 6 h post-lysis, until effective oral anticoagulation	30	APSAC: 32/502 (6.4) Placebo: 61/502 (12.2) 0.53 (0.35–0.79)	
ISIS-2[91] 1985–1987	STE 61 BBB 4 ST-segment depression 7 Other 25 Normal 2	0–6 (63); 7–12 (23); 13–24 (14)	Streptokinase 1.5 × 10^6 U over 1 h	Placebo	Aspirin (50%)	No	35	Streptokinase: †791/8,592 (9.2) Placebo: †1,029/8,595 (12.0) OR, 25% SD 4%	†Vascular mortality (primary end point); nonvascular mortality 4/8,592 vs 4/8,595
ASSET[30] 1986–1988	STE BBB ST-segment depression, or Other 82 Normal 18	0–6 (100)	tPA 100 mg over 3 h	Placebo	No	Yes, IV 5,000 U + 1,000 U/h for 24 h	30	tPA: 182/2,516 (7.2) Placebo: 245/2,495 (9.8); 0.74 (0.61–0.89)	
USIM[31] 1986–1988	STE 89 BBB 0 ST-segment depression 0 Other 10 Normal 0	0–6 (100)	Urokinase 1 × 10^6 U bolus repeated at 60 min	Open	No	Yes, IV 10000 U + 1,000 U/h for 48 h	In hospital (9–16 in > 90%)	Urokinase: 90/1,123 (8.0) Control: 89/1,073 (8.3); 0.96 (0.70–1.31)	
ISIS-3[32] 1989–1991	STE 30 BBB 8 ST-segment depression 19 Other 25 Normal 17	0–6 (54); 7–12 (28); 13–24 (18)	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	Open	Aspirin	50% SC 12500 U bid for 7 d	35	Fibrinolytic: 400/4,601 (8.7) Control: 375/4,557 (8.2)	37,000 patients considered to have "certain" indication for lysis and randomized between streptokinase, tPA, and APSAC not included; 9,158 patients with "uncertain" indication for lysis allocated to lysis (1/3 to each lytic; combined in this report) or open control

Table 2—*Continued*

Study Year	Entry ECG Features %	Time From Symptom Onset to Randomization, h (%)	Fibrinolytic Regimen	Control	Routine Antiplatelet	Routine Heparin, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total Patients (%); RR (95% CI)	Comments
EMERAS[33] 1988–1991	STE 76 BBB 6 ST-segment depression 4 Other 12 Normal 2	†0–6 (15); 7–12 (46); 13–24 (40)	Streptokinase 1.5 × 10^6 U over 1 h	Placebo	Aspirin	No	In hospital	Streptokinase: 269/2,257 (11.9) Placebo: 282/2,277 (12.4)	After ISIS-2[91] results became available, only patients presenting > 6 h after symptom onset were randomized
LATE[34] 1989–1992	STE 55 BBB 2 ST-segment depression 12 Other 30 Normal 0	†0–6 (2); 7–12 (38); 13–24 (60)	tPA 100 mg over 3 h	Placebo	Aspirin	64% IV 5,000 U (bolus if given concurrently with tPA/ placebo or 2 boluses given pre and 3 h post-tPA/placebo) + 1,000 U/h for 48 h	35	tPA: 397/2,836 (8.9) Placebo: 444/2,875 (10.3); 0.86 (0.72–1.00)	Patients presenting ≤ 6 h after symptom onset were to be excluded

*APSAC = anisoylated plasminogen streptokinase activator complex; other = other ECG abnormalities.
†Adapted from FTT Collaborative Group.[42]

including when the analysis was limited to patients receiving reperfusion therapy (RR, 0.52; 95% CI, 0.25 to 1.08; p = 0.08).[55]

In the FTT overview,[42] 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 h of symptom onset. For those presenting at 7 to 12 h, there were approximately 20 deaths prevented per 1,000 patients treated; beyond 12 h, there was a statistically uncertain benefit of about 10 per 1,000. While the FTT overview[42] 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[63] of 22 trials (n = 50,246) suggested a nonlinear relation. The beneficial effect of fibrinolysis was substantially higher in patients presenting within 2 h 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[42] 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 < 0.01), there are some important caveats to consider. First, the trials included[27–34] in the FTT Collaborative Group overview[42] 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,[64] 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.[65] An ECG substudy[66] from the HERO-2 trial[67] (n = 300) suggested that the presence of left BBB in a patient with symptoms compatible with acute MI should not in itself be regarded as an independent marker of high risk; the authors proposed that patients with left BBB could be risk stratified by the presence or absence of concordant ST-segment elevation or lead

Table 3—*IV Fibrinolytic Therapy for Patients With STE MI: Summary Evidence Profile (Section 1.1)*

	No. of Deaths†/Patients (%)		Effect		
No. of Studies*	Fibrinolysis	Control‡	Proportional Reduction, % (95% CI)	Events Prevented per 1,000 Treated, No. (SD)	Quality
9	2,820/29,315 (9.6)	3,357/29,285 (11.5)	18 (13–23)	18 (3)	High

*Includes all randomized trials of > 1,000 patients; adapted from FTT Collaborative Group.[42]
†Days 0 to 35.
‡Placebo in six of nine trials.

Table 4—*Randomized Trials of Prehospital vs In-Hospital IV Fibrinolytic Therapy in Suspected Acute MI: Clinical Description and Results (Section 1.1)**

Study†	Provider	Inclusion	Fibrinolytic Regimen	Control	Time From Symptom Onset to Fibrinolysis, min	Mortality, No./Total (%); OR (95% CI)
Castaigne et al[49] 1989	Mobile ICU	Age < 75 yr, chest pain onset < 6 h, and STE	APSAC 30 U over > 4 min	Placebo	Prehospital: 131 In hospital: 180 (median)	Prehospital: 3/57 (5.3) In hospital: 3/43 (7.0); 0.74 (0.14–3.86)
EMIP Group[50] 1993	Mobile ICU	Chest pain onset < 6 h and STE or QRS> 0.12 s or isolated ST-segment depression or tall T-waves with coronary artery disease	APSAC 30 U over 4–5 min	Placebo	Prehospital: 130 In hospital: 190 (median)	Prehospital: 251/2750 (9.1) In hospital: 284/2719 (10.4); 0.86 (0.72–1.03)
GREAT Group[51]1992	General practitioners	Clinical suspicion of AMI, chest pain onset < 4 h, and transportation to ICU ≤ 6 h of symptom onset	APSAC 30 U over 5 min	Placebo	Prehospital: 101 In hospital: 240 (median)	Prehospital: 11/163 (6.8) In hospital: 17/148 (11.5); 0.56 (0.25–1.23)
MITI Project Group[54]1993	Paramedics	Age < 75 yr, chest pain onset < 6 h, and STE (confirmed by physician)	tPA 100 mg over 3 h	Placebo	Prehospital: 77 In hospital: 110 (median)	Prehospital: 10/175 (5.7) In hospital: 15/175 (8.6); 0.69 (0.30–1.57)
Roth et al[52] 1990	Mobile ICU	Age 73 yr, chest pain onset < 4 h, and STE	tPA 120 mg over 6 h	Open	Prehospital: 94 In hospital: 137 (median)	Prehospital: 4/72 (5.6) In hospital: 3/44 (6.8); 0.80 (0.17–3.77)
Schofer et al[53] 1990	Mobile ICU	Age ≤ 70 yr, chest pain onset < 4 h, and STE	Urokinase 2×10^6 U bolus	Placebo	Prehospital: 85 In hospital: 137 (median)	Prehospital: 1.40 (2.5) In hospital: 2/38 (5.3); 0.46 (0.04–5.31)

*Adapted from Morrison et al.[57] AMI = acute MI; see Table 2 for other abbreviations.
†Year of publication.

Table 5—*Prehospital vs In-Hospital IV Fibrinolytic Therapy for Patients With STE MI, Summary of Findings: Summary Evidence Profile (Section 1.1)*

	No. of Deaths†/Patients (%)		Effect		
No. of Studies*	Prehospital‡	In Hospital	OR (95% CI)	Events Prevented per 1,000 Treated, No. (SD)	Quality
6	280/3,257 (8.6)	324/3,167 (10.2)	0.83 (0.70–0.98)	16 (7)	High

*Includes all randomized trials meeting inclusion criteria for the systematic review and with an in-hospital primary end point by Morrison et al.[57]
†In hospital.
‡Placebo in five of six trials.

V_1–V_3 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).[66] 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.[42,68,69] However, fibrinolytic therapy may be appropriate when there is marked ST-segment depression confined to leads V_1–V_4 and accompanied by tall R waves in the right precordial leads and upright T waves indicative of a

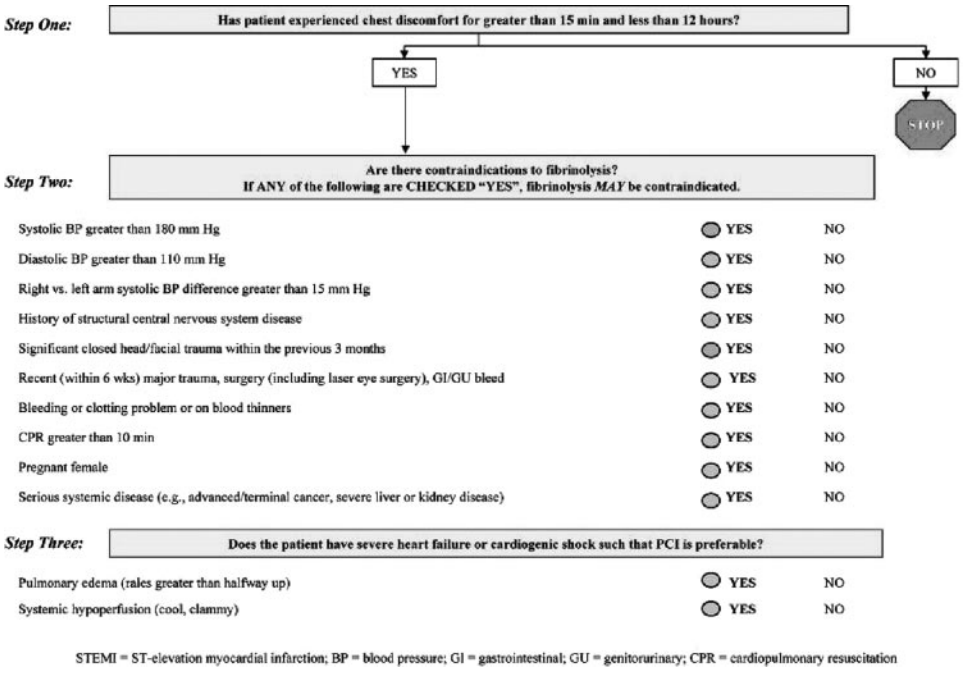

FIGURE 1. Reperfusion checklist for evaluation of the patient with STE MI. From Antman et al[6] (Reprinted with permission ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction, 2004, American Heart Association, Inc.).

true posterior injury current and possibly circumflex coronary occlusion.[70] Confirmatory data from posterior leads (*ie*, V_7–V_9)[71] as well as emergent echocardiography,[72] 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.[6] Hemorrhage represents the most important risk of fibrinolytic therapy, especially intracranial hemhorrage (ICH), which is fatal in up to two thirds of patients. The FTT[42] 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 trial[37] (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 (*eg*, age, weight, hypertension on admission) and also illustrate the impact of certain therapeutic decisions (*eg*, selection of streptokinase vs tissue plasminogen activator [tPA]).[6]

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

Absolute contraindications
Any prior ICH
Known structural cerebral vascular lesion (*eg*, arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 mo except acute ischemic stroke within 3 h
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 mo
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg)
History of prior ischemic stroke > 3 mo, dementia, or known intracranial pathology not covered in contraindications
Traumatic or prolonged (> 10 min) cardiopulmonary resuscitation or major surgery (≤ 3 wk)
Recent (≤ 2–4 wk) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase: prior exposure (> 5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of vitamin K antagonists: the higher the international normalized ratio, the higher the risk of bleeding

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

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-IIa,[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-9B[82] (1.87 to 1.07%), GUSTO-IIb[83] (0.92 to 0.71%), and TIMI 10B[81] (2.8 to 1.16%). More recent trials like ASSENT-2,[41] ASSENT-3,[84] InTIME-II,[85] and ExTRACT-TIMI 25[86] 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 trial[85] 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 Group[42] 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 al[89] 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 study[41] 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 overview[90] 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 trials[27,91] 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; $p = 0.008$)[92] and 10 years,[93] respectively. Similarly, the second International Study of Infarct Survival study[91] 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

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

Agent	Fibrin Specific	Metabolism	Half-Life, min	Mode of Action	Allergic Reactions	Dosing	Hospital Cost/Dose†
Streptokinase	—	Hepatic	18–23	Activator complex	Yes	1.5×10^6 U over 60 min	$613
Alteplase, duteplase (tPA)	++	Hepatic	3–8	Direct	No	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)	$2,974
Reteplase	+	Renal	15–18	Direct	No	10×10^6 U × 2 boluses each over 2 min given 30 min apart	$2,750
Tenecteplase	+++	Hepatic	18–20	Direct	No	30 mg for weight < 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	$2,833‡

*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.

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 trial[33] was altered to include only patients who presented at least 6 h after but within 24 h of symptom onset, once the ISIS-2 results[91] 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 colleagues[96] 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 2[35]/International Study Group[36] 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 trial[32] 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-2[35]/International Study Group[36] trials, patients were also randomized to two different antithrombotic regimens; in ISIS-3[32] 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 8—*Large (> 1,000 Patients) Randomized Trials of One IV Fibrinolytic vs Another IV Fibrinolytic in Suspected Acute MI: Clinical Description and Results (Section 1.1.1)</*

Study Year	Entry ECG Features %	Time from Symptom Onset to Randomization, h (%)	Fibrinolytic Regimens	Blinded	Routine Aspirin Dose	Routine Heparin, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
GISSI-2[35] 1990	STE 100	0–6 (100)	Streptokinase 1.5 × 10^6 U over 30–60 min tPA 100 mg over 3 h	No	300–325 mg/d	50%, SC 12,500 U bid	35	Streptokinase: 536/6,199 (8.6); tPA: 556/6,182 (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 > 10): 1,394/6,199 (22.5%) vs 1,428/6,182 (23.1%), RR 1.04 (95% CI 0.95–1.13)
ISG[36] 1990	STE 100	0–6 (97) > 6 (3)	Streptokinase 1.5 × 10^6 U over 30–60 min tPA 100 mg over 3 h	No	300–325 mg/d	50%, SC 12,500 U bid	35	Streptokinase: 887/10,396 (8.5) tPA: 929/10,372 (8.9) RR 1.05 (0.95–1.16)	Includes 12,490 patients in the GISSI-2 trial[35] and 8,401 patients recruited in 13 other countries (351/4,197 [8.4%] vs 373/4,190 [8.9%])
ISIS-3[32] 1992	STE 77 Normal 3	0–6 (63) > 6 (37)	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	No	162 mg/d	50% SC 12,500 U starting 4 h post-randomization and then bid for 7 d or until discharge	35	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 "clear" or "uncertain" indication for lysis; 12% of patients received IV, non-trial allocated heparin
GUSTO-I[37] 1993	STE 100	0–6 (100)	Streptokinase 1.5 × 10^6 U over 1 h or 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 (1 mg/kg [maximum 90 mg] over 1 h with 10% given as bolus) plus streptokinase (1 × 10^6 U over 1 h)	No	160–325 mg/d	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 > 80 kg), target APTT 60–85 s	30	Streptokinase + SC UFH: /9,796 (7.2) Streptokinase + IV UFH: /10,377 (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 patientsto receive IV UFH

Table 8—*Continued*

Study Year	Entry ECG Features %	Time from Symptom Onset to Randomization, h (%)	Fibrinolytic Regimens	Blinded	Routine Aspirin Dose	Routine Heparin, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
COBALT[40] 1997	STE 100	0–6 (100)	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 < 60 kg) 30 min later	No	80–325 mg/d (minimum initial 160 mg dose)	IV 5,000 U + 1,000 U/h (1,200 U/h for weight > 80 kg), target APTT 60–85 s	30	Accelerated tPA: 270/3,584 (7.53) Double-bolus tPA: 286/3,585 (7.98) Absolute difference + 0.44%, 1-sided 95% upper boundary 1.49	Mortality difference exceeds prespecified boundary of 0.40; equivalence not met
INJECT[39] 1995	STE 98 BBB 2	0–6 (80) 7–12 (20)	Streptokinase 1.5×10^6 U over 1 h or reteplase 10×10^6 U boluses given 30 min apart	Yes	75–150 mg/d (250–320 mg initial dose)	IV 5,000 U + 1,000 U/h starting 60 min post-lysis for ≥ 24 h, target APTT 1.5–2 times normal	35	Streptokinase: 285/3,006 (9.53) Reteplase: 270/3,004 (9.02) Absolute difference −0.51% (90% CI−1.76%, +0.71%)	Mortality difference within prespecified boundary; equivalence met
GUSTO-III[38] 1997	STE 96 BBB 3	0–6 (100)	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	No	160–325 mg/d (160 mg initial dose)	IV 5,000 U + 1000 U/h (800 U/h for weight < 80 kg), target APTT 50–70 s	30	tPA: /4921 (7.24) Reteplase: /10138 (7.47) OR 1.03 (0.91–1.18)	
ASSENT-II[84] 1999	STE 95 left BBB 5	0–6 (100)	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 < 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	Yes	150–325 mg/d	IV 4,000 U + 800 U/h for weight ≤ 67 kg and IV 5,000 U + 1000 U/h for weight > 67 kg, target APTT 50–75 s for 48–72 h	30	tPA: /8,488 (6.151) Tenecteplase: /8461 (6.179) Absolute difference + 0.028 (95% CI−0.554–0.609)	Mortality difference within prespecified boundary; equivalence met

*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-3[32] 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 investigators[37] (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 investigators[37] 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 alteplase[37] 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 trial[99] comparing accelerated alteplase, anistreplase, and their combination (all patients received IV UFH).

The benefits of accelerated alteplase seen in the GUSTO-I[100] and TIMI-4[99] angiographic trials and the superior outcome in the GUSTO-I trial[37] vs the lack of mortality benefit seen in GISSI-2[35]/International Study Group[36] and ISIS-3[32] 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-2[35]/International Study Group[36] and ISIS-3[32] 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-2[35]/International Study Group[36] and ISIS-3[32] trials.

The Late Assessment of Thrombolytic Efficacy study[34] 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 trial[33] (with streptokinase), but consistent with the larger GISSI-1[27] and ISIS-2[91] 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[40] (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 STE MI.[37]

1.1.5 Reteplase

The International Joint Efficacy of Comparison of Thrombolytic study[39] 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 0.88%).

Two angiographic studies[108,109] 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[108] and an accelerated regimen in RAPID 2[109]). 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[100]; 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.[108,109]

The Global Use of Strategies To Open Occluded Coronary Arteries 3 study[38] 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.[38] 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[37]), 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[110] 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,[111] B,[81,112] and the Assessment of the Safety and Efficacy of a New Thrombolytic Agent I[113] 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,[41] a large trial of patients (n = 16,950) with acute STE MI 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%).[114]

There has been significant previous debate regarding the risk of ICH with bolus vs infusion fibrinolytic therapy.[115–117] 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[115,117] 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.**

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.[118–120] Microvascular damage occurs as a consequence of downstream embolization of platelet microemboli and thrombi followed 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).[91] 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[121] including the ISIS-2 trial[91] and 14 other trials (n = 19,288) demonstrated a significant odds reduction (30%; SE, 4%) in patients allocated antiplatelet (mainly aspirin[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).[121] With the exception of clopidogrel (see following), direct comparisons of aspirin with either other oral antiplatelet agents[127–129] or aspirin plus another oral antiplatelet agent[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[131]; as noted above, the largest trial (ISIS-2[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[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[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[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; $p = 1.00$).[135]

The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study 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.[133] Patients pre-

Table 9—*Randomized Trials of Aspirin Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.1)**

Study Year	Patient and ECG Features (%)	Time From Symptom Onset to Randomization h	Aspirin Regimen	Control	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
ISIS-Pilot[125] 1987	Suspected MI, symptom onset ≤ 24 h	Aspirin 6.7 h Placebo 6.4 h†	Enteric-coated 325 mg on alternate days for 28 d	Placebo	30	Aspirin: 25/313 (8.0) Placebo: 35/306 (11.4)	
ISIS-2[91] 1988	Suspected MI, symptom onset ≤ 24 h, STE 61 BBB 4 ST-segment depression 7 other 25 normal 2	0–6 (63%) 7–12 (23%) 13–24 (14%)		Placebo	35	Aspirin: 817/8,587 (9.5) Placebo: 1,033/8,600 (12.0)	
Verheught et al[122] 1990	First anterior MI (STE > 2 mm in precordial leads and absence of Q waves)	Aspirin 244 ± 42 min Placebo 248 ± 48 min‡	100 mg	Placebo	3 mo	Aspirin: 10/50 (20) Placebo: 12/50 (24) h	Fibrinolysis administered to patients < 70 yr who had symptoms < 4
Rasmanis et al[123] 1988	Acute MI, symptom onset ≤ 24 h	Mean 9.3 h	500 mg in buffered water solution 12 h post-admission and every third day thereafter		30	Aspirin: 0/10 (0) Placebo: 1/10† (10)	Patient died of pneumonia; no cardiac deaths
Johannessen et al[124] 1989			150 mg		14	Aspirin: 0/11 (0) Placebo: 0/9 (0)	
Boehringer Ingelheim (unpublished)† 1976	Information not available	Information not available	1,320 mg	Information not available	14	Aspirin: 1/25 (4.0) Placebo: 1/28 (3.6)	Internal report: Asasantin DVT nach Myokardinfarkt: Bracknell, Berkshire: Boehringer Ingelheim§
Meijer et al (APRICOT)[126] 1993	Age < 70 yr, STE < 4 h treated with fibrinolysis with patient IRA	Aspirin ~ 27 Placebo ~ 24	325 mg/d	Placebo	3 mo	Aspirin: 1/107 (0.9) Placebo: 2/95 (2.1)	Approximate mean time from symptom onset to angiography, after which patients were randomized

*Adapted from Antithrombotic Trialists' Collaboration.[121]

†Mean values.

‡Mean ± SD.

§Ingelheim, Germany.

Table 10—*Antiplatelet Therapy for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.1)*

No. of Studies*	Deaths†/Total Patients, No. (%)		Effect		Quality
	Antiplatelet	Control	OR (95% CI)	Events Prevented per 1,000 Treated (SEM)	
15	886/9,856 (9.2)	1,112/9,644 (11.5)	0.76 (0.69–0.83)	24 (4)	High

*Includes all randomized trials meeting inclusion criteria for the quantitative review by the Antithrombotic Trialists' Collaboration.[121]
†Mean 1-mo duration of treatment.

sented 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 trial[136] 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-**

Table 11—*Randomized Trials of Clopidogrel Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.2)**

Study Year	Patient and ECG Features %	Time From Symptom Onset to Randomization, h	Fibrinolytic Therapy	Antithrombotic Therapy	Aspirin Regimen	Control	Duration of Follow-up	Mortality, No./Total (%)	Comments
CLARITY-TIMI 28[132] 2003–2004	Suspected MI, symptom onset ≤ 12 h, 18–75 yr, STE or LBBB 100	Median 2.7	99.7% (68.8% fibrin-specific)	UFH 45.8% LMWH 29.6% both 5%; neither 19.6%	150–325 mg initial; 75–162 mg/d	Placebo	30 d	Clopidogrel: 45/1,752 (2.6) Placebo: 38/1,739 (2.2) OR 1.17 (95% CI 0.75–1.82)	Primary outcome TIMI flow grade 0–1 (angiography median 84 h post-randomization), death, or reinfarction: clopidogrel 262/1752 (15.0%) vs placebo 377/1,739 (21.7%), OR 0.64 (95% CI 0.53–0.76)
COMMIT[133] 1999–2005	Suspected MI, symptom onset ≤ 24 h, STE 87 BBB 6 ST-segment depression 7	< 6 (34; 6 to < 13 (33); 13–24 (33)	50% pre-randomization (mainly urokinase)	75% in-hospital (mainly heparin)	162 mg/d	Placebo	Hospital discharge or 28 d	Clopidogrel: 1,726/22,961 (7.5) Placebo: 1,845/22,891 (8.1) OR 0.93 (95% CI 0.87–0.99)	Coprimary outcome death, reinfarction, or stroke: clopidogrel 2,121/22,961 (9.2%) vs placebo 2,310/22,891 (10.1%), OR 0.91 (95% CI 0.86–0.97)

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[144] 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), 19 ± 5 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[144] also examined the role of heparin in the presence of aspirin. Approximately 68,000 patients have been randomly assigned in seven trials[32,36,91,91,125,145–147] 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

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	Clopidogrel	Placebo	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
2	1771/24,713 (7.2)	1,883/24,630 (7.6)	0.93 (0.87–1.00)	5 (2)	High

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	UFH	Control	Odds Reduction, % (SE) or OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
Trials with no routine aspirin, No.*†					
21	284/2,684 (11.4)	378/2,775 (14.9)	25 (8)	35 (11)	High
Trials with routine aspirin*‡					
6	2,932/34,035 (8.6)	3,092/34,055 (9.1)	6 (3)	5 (2)	High
Trials with IV UFH and routine fibrinolytic therapy§					
6	45/878 (5.1)	48/857 (5.6)	0.91 (0.59–1.39)	5 (11)	High

*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 al[150]; follow-up in hospital.

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

Most of this evidence about adding heparin to aspirin therapy comes from the patients (n = 62,067) who received fibrinolytic therapy in the GISSI-2[148] and ISIS-3[32] trials (Table 13). 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 effect of heparin on mortality at 35 days (2 ± 2 fewer deaths per 1,000 patients) or at 6 months (1 ± 3 fewer deaths per 1,000 patients).[32]

Six randomized controlled trials (Table 14) have compared IV UFH with no heparin in STE MI treated with fibrinolysis (n = 1,735).[150] In-hospital mortality was similar (5.1% vs 5.6%; OR, 0.91; 95% CI, 0.59 to 1.39), as were rates of recurrent ischemia and reinfarction. The rates of total stroke, ICH, and severe bleeding were similar in patients allocated to heparin; however, the risk of any severity of bleeding was significantly higher (22.7% vs 16.2%; OR, 1.55; 95% CI, 1.21 to 1.98). 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 trial[32] 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 s[151]). 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 trials[154–156] 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 trials[37,38,82,83] with

Table 14—*Selected Randomized Trials of UFH Therapy vs Control in Suspected Acute MI: Clinical Description and Results (Section 2.3)*

Study Year	Patient and ECG Features %	Heparin Regimen, Dose, Duration, APTT Adjustment	Blinded	Routine Aspirin Dose	Fibrinolytic(s)	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
ISIS-Pilot[125] 1987	Suspected MI, symptom onset ≤ 24 h, no specific ECG criteria	IV 1,000 U/h for 48 h, starting 12 h after the end of streptokinase infusion, no APTT adjustment	No	Enteric-coated 325 mg on alternate days for 28 d (50%)	Streptokinase (2/3)	In-hospital (median 9)	Heparin: 25/314 (8.0) Control: 26/305 (8.5)	
GISSI-2[35] 1990	Symptom onset ≤ 6 h, STE 100	SC 12,500 U bid, starting 12 h after initiation of fibrinolytic, continued until hospital discharge, no APTT adjustment	No	300–325 mg/d	Streptokinase (50%), tPA over 3 h (50%)	35	Heparin: 518/6175 (8.3) Control: 574/6,206 (9.3)	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 > 10): 1,403/6,175 (22.7%) vs 1,419/6,206 (22.9%), RR 0.99 (95% CI 0.91–1.08)
ISG[36] 1990	Symptom onset ≤ 6 h, STE 100	SC 12,500 U bid, starting 12 h after initiation of fibrinolytic, continued until hospital discharge, no APTT adjustment	No	300–325 mg/d	Streptokinase (50%), tPA over 3 h (50%)	35	Heparin: 884/10361 (8.5) Control: 932/10407 (8.9) RR 0.95 (0.86–1.04)	Includes 12,490 patients in the GISSI-2 trial[35] 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
Bleich et al[152] 1990	Symptom onset ≤ 6 h; STE 100	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	No	None	tPA over 3 h	In-hospital	Heparin: 6/46 (13.0) Control: 5/49 (10.2)	
Hsia et al (HART)[153] 1990	Age ≤ 75 yr; symptom onset ≤ 6 h; STE 100	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	No	80 mg/d in patients not receiving heparin	tPA over 4 h	7	Heparin: 2/106 (1.9) Control (aspirin): 4/99 (4.0)	

Table 14—*Continued*

Study Year	Patient and ECG Features %	Heparin Regimen, Dose, Duration, APTT Adjustment	Blinded	Routine Aspirin Dose	Fibrinolytic(s)	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
ISIS-3[268] 1992	Suspected MI; symptom onset ≤ 24 h; STE 77 BBB 4 ST-segment depression 7 Other 8 Normal 3	SC 12,500 U starting 4 h after randomization and then bid for 7 d or until discharge; no APTT adjustment	No	162 mg/d	Streptokinase (1/3), tPA over 4 h (1/3), APSAC (1/3)	35	Heparin: 2,132/20,656 (10.3) Control: 2,189/20,643 (10.6)	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
de Bono et al (ECSG)[145] 1992	Age ≤ 70 yr; symptom onset ≤ 6 h; STE 100	IV 5,000 U bolus followed by 1,000 U/h until catheter at 48–120 h, no APTT adjustment	Yes	250 mg IV bolus or 300 mg po, then 75–125 mg po on alternate days	tPA over 3 h	In-hospital	Heparin: 9/324 (2.8) Placebo: 11/320 (3.4)	652 patients randomized; data available for 644
Col et al (OSIRIS)[146] 1992	Symptom onset ≤ 6 h; STE 100	IV 10,000 U bolus before lysis followed by 1,000 U/h for 24 h; APTT adjustment unknown	Yes	200 mg/d	Streptokinase	In-hospital	Heparin: 1/64 (1.6) Placebo: 3/64 (4.7)	
O'Connor et al (DUCCS 1)[147] 1994	Age ≤ 85 yr; symptom onset ≤ 12 h; STE 100	IV 15 U/kg/h 4 h after lysis for 5 d; adjusted to target APTT 50–90 s	No	325 mg/d	APSAC	14	Heparin: 12/128 (9.4) Control: 8/122 (6.6)	

*Adapted from Collins et al,[144] Collins et al,[149] and Mahaffey et al.[150]

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).[77,81,154,155,157] 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.[6,78] In the ASSENT-3 trial,[84] this suggested reduced-dose, weight-adjusted IV UFH regimen (target APTT, 50 to 70 s) was employed and resulted in similar ICH (30-day mortality, and recurrent MI) rates but less bleeding than that observed in the ASSENT-2 trial[41] (which used a 4,000-U bolus and 800 U/h infusion for patients ≤ 67 kg and a 5,000-U bolus and 1,000 U/h infusion for patients > 67 kg; target APTT, 50 to 75 s).[158] An APTT measurement and dose adjustment was made at 3 h,[41,84] 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.[159] Consensus conferences of The College of American Pathologists,[160] and the American College of Chest Physicians,[161] and other sources,[162–164] 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[165] 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,[166,167] 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,[86] fondaparinux;[168] 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,[169–172] 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.[173] 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[174] (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[175] 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,[175] a randomized comparison[176] 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 (13% 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 UFH[177,178] (see chapter by Hirsh et al in this supplement). Several small randomized studies have examined rates of IRA patency[179–181] and reocclusion,[180,182,183] left ventricular thrombus formation/arterial thromboembolism,[184] and clinical outcomes[181–183,185,186] with LMWH[178] as compared to placebo[179,182,184,185] (Tables 15, 16) or UFH[180,181,183,186] (Tables 17, 18). More recently, moderate-to-large randomized clinical outcome trials comparing LMWH to placebo[187] (Tables 15, 16) and to UFH[84,86,188] (Tables 17, 18) in the setting of fibrinolysis have been completed.

Combined, four small studies[179,182,184,185] ($n = 1,376$) comparing LMWH to placebo (as adjunctive therapy to fibrinolysis in two studies[179,182] and starting LMWH 5 to 8 days after lysis in two studies[184,185]) 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 Evaluation[187] 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, 0.85 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)*

Study Year	Patient and ECG Features %	Heparin Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Reperfusion Therapy	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Kontny et al (FRAMI)[184] 1997	Suspected evolving anterior Q wave MI (Q waves or STE), symptom onset ≤ 6 h	Dalteparin 150 U/kg (maximum 100 kg) SC, started 8 h after lysis, then q12h, continued until hospital discharge	Yes	300 mg initially, 160 mg/d	Streptokinase	9 ± 2	Dalteparin: 21/388 (5.4) Placebo: 23/388 (5.9)	Warfarin instead of aspirin in patients considered at high risk of thromboembolic events (*eg*, thrombus, severe wall motion abnormalities)
Frostfeldt et al (BIOMACS II)[179] 1999	Symptom onset ≤ 12 h, STE or left BBB	Dalteparin 100 U/kg (maximum 100 kg) SC, started before lysis, then 120 U/kg 12 h later (maximum 10,000 U)	Yes	300 mg initially, 75 mg/d thereafter	Streptokinase	21	Dalteparin: 4/54 (7.4) Placebo: 6/47 (12.8)	
Simoons et al (AMI-SK)[182] 2002	Symptom onset ≤ 12 h STE 100	Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for 3–8 d	Yes	100–325 mg/d	Streptokinase	30	Enoxaparin: 17/253 (6.7) Placebo: 17/243 (7.0)	
CREATE[187] 2005	Symptom onset ≤ 12 h STE or new left BBB	Reviparin 3,436 U for patients < 50 kg, 5,133 U for patients 50–75 kg, and 6,871 U for patients > 75 kg SC q12h	Yes	97% of patients, dose unknown	Fibrinolysis (74%), primary PCI (9%)	30	Reviparin: 766/7,780 (9.8) Placebo: 877/7,790 (11.3) HR 0.87 (95% CI 0.79–0.96)	Open-label UFH used in patients undergoing primary PCI with study medication initiated 1 h after sheath removal

Table 16—*LMWH vs Control for Patients With Suspected Acute MI: Summary Evidence Profile (Section 2.4)*

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	LMWH	Placebo	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
4	808/8,475 (9.5)	923/8,468 (10.9)	0.86 (0.78–0.95)	14 (5)	High

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 = 3,325) 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 trials[62,84,181,186,190] have compared enoxaparin to UFH as an adjunct to fibrinolysis (including one study[62] as a prehospital adjunct to tenectaplase) and one study[191] 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 0.89%; OR, 1.30; 95% CI, 0.84 to 2.03).[189] This overview[189] did not include the small ASSENT PLUS study[183] (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 parnaparin 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 tenecteplase and enoxaparin for up to 7 days (n = 2,040), half-dose tenecteplase with weight-adjusted low-dose UFH and a 12-h infusion of the GP IIb/IIIa inhibitor abciximab (n = 2017), 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 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)*

Study Year	Patient and ECG Features %	LMWH Regimen, Dose, Duration	UFH Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Fibrinolytic(s)	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Ross et al (HART II)[190] 2001	Symptom onset ≤ 12 h STE 100	Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for ≥ 3 d	IV bolus 4,000 U for weight < 67 kg, 5,000 U for weight ≥ 67 kg, followed by infusion 15 U/kg/h for ≥ 3 d, adjusted to target APTT 2–2.5 times control	No	Yes, dose unknown	tPA	30	Enoxaparin: 9/196 (4.5) UFH: 10/197 (5.0)	
ASSENT-3[84] 2001	Symptom onset ≤ 6 h; STE or left BBB	Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for ≤ 7 d	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	No	150–325 mg/d	Tenecteplase	30	Enoxaparin: 109/2,037 (5.4) Lower-dose UFH + abciximab: 133/2,017 (6.6) UFH: 122/2,038 (6.0)	Boluses administered before fibrinolysis; initial APTT sample drawn after 3 h
Baird et al[186] 2002	STE; receiving fibrinolysis	Enoxaparin 40 mg IV bolus then 40 mg SC q8h for 4 d	IV bolus 5,000 U, followed by 3,000 U per 24 h, adjusted to target APTT 2–2.5 times normal	No	75–300 mg/d	Streptokinase, anistreplase, or tPA (43% pre-hospital)	90	Enoxaparin: 9/149 (6.0) UFH: 16/151 (10.6)	Following the 4-d study period, patients at risk of left ventricular mural thrombosis (anterior MI) received 5,000 to 10,000-U IV boluses of UFH q6h for 3 d; cardiac death
Antman et al (ENTIRE-TIMI 23)[181] 2002	Age ≤ 75 yr; symptom onset ≤ 6 h; STE	Enoxaparin ± 30 mg IV bolus, then 1 mg/kg SC q12h for 2–8 d	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 ≥ 36 h, adjusted to target APTT 1.5–2.5 times control	No	≥160 mg po or 250–500 mg IV followed by 100–325 mg/d	Tenecteplase	30	Enoxaparin: 10/324 (3.1) UFH: 5/159 (3.1)	Half-dose tenecteplase in patients receiving abciximab
Cohen et al (TETAMI)[191] 2003	STE MI and deemed unsuitable for fibrinolysis or primary PCI	Enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h for 2–8 d	70 U/kg IV bolus, then 15 U/kg/h for 2–8 d, adjusted to target APTT	Yes	100–325 mg/d	None	30	Enoxaparin: 42/604 (7.0) UFH: 41/620 (6.6)	Patients also randomized to receive tirofiban or placebo

Table 17—*Continued*

Study Year	Patient and ECG Features %	LMWH Regimen, Dose, Duration	UFH Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Fibrinolytic(s)	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Wallentin et al (ASSENT Plus)[269] 2003	Symptom onset ≤ 6 h, STE or left BBB	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	IV bolus 4,000 U for weight ≤ 67 kg, 5,000 U for weight > 67 kg, followed by infusion 800 U/h (≤ 67 kg) or 1,000 U/h (weight > 67 kg) for 48 h, adjusted to target APTT 50–75 s	No	150–325 mg/d	tPA	30	Dalteparin: 9/221 (4.1) UFH: 11/212 (5.2)	
Zhang et al[192] 2004	Symptom onset ≤ 12 h; STE	Parnaparin 0.4 mL SC 12 h after lysis and then q12h for 7 d	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	No	75–150 mg/d	Yes, agents unknown	45	Parnaparin: 12/96 (12.5) UFH: 14/90 (15.6)	
Wallentin et al (ASSENT-3 PLUS)[62] 2003	Symptom onset ≤ 6 h; STE or left BBB	Enoxaparin 30 mg IV bolus, then 1 mg/kg (maximum 100 mg for first 2 doses) SC q12h for ≤ 7 d	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	No	150–325 mg initial, then 100–325 mg/d	Tenecteplase	30	Enoxaparin: 61/817 (7.5) UFH: 49/818 (6.0) RR 0.80 (95% CI 0.56–1.15)	Administered before hospital
Antman et al (ExTRACT-TIMI 25)[86] 2006	Symptom onset ≤ 6 h; STE or left BBB	Enoxaparin 30 mg IV bolus for age < 75 yr, then 1 mg/kg for age < 75 yr or 0.75 mg/kg for age ≥ 75 yr (maximum 100 mg for age < 75 yr or maximum 75 mg for age ≥ 75 yr for first 2 doses) SC q12h for ≤ 7 d	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	Yes	150–325 mg po or 500 mg IV initial, then 75–325 mg/d	Tenecteplase (20%), tPA (55%), reteplase (6%), or streptokinase (20%)	30	Enoxaparin: 708/10,256 (6.9) UFH: 765/10,233 (7.5) RR 0.92 (95% CI 0.84–1.02)	For patients with an estimated creatinine clearance < 30 mL/min, dose was modified to 1 mg/kg q24h

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	LMWH	UFH	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
8	708/14,700 (4.8)	1,066/16,535 (6.4)	0.73 (0.67–0.81)	16 (3)	High

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 trial[62] 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

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 trial[191] 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 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 md/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 STE[196] (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 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 study[168] 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 fibrinolytics 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 48 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 therapy.[168] 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)*

Study Year	Patient and ECG Features %	Fondaparinux Regimen, Dose, Duration	UFH Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Reperfusion Therapy	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Coussement et al (PENTALYSE)[197] 2001	Age 21–75 yr, symptom onset ≤ 6 h, STE 100	IV bolus 4 mg (or 6 mg if weight > 90 kg) or 8 mg (or 6 mg if weight < 60 kg or 10 mg if weight > 90 kg) or 12 mg (or 10 mg if weight < 60 kg), then SC daily for 5–7 d	IV bolus 4,000 U for weight ≤ 67 kg, 5,000 U for weight > 67 kg, followed by infusion 800 U/h (≤ 67 kg) or 1,000 U/h (weight > 67 kg) for 48–72 h, adjusted to target APTT 50–75 s	No	150–325 mg/d	tPA	30	Fondaparinux: 6/241 (2.5) UFH: 1/85 (1.2)	Low (2/81), medium (2/77), and high (2/83) doses combined
OASIS-6 Trial Group[168]	Symptom onset ≤ 12 h STE 100	2.5 mg (initial IV bolus for patients without an indication for UFH) SC daily for up to 8 d or hospital discharge	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%)	Yes	Yes, dose uncertain	Fibrinolysis (45%), primary PCI (29%), none (24%)	30	Fondaparinux: 470/6,036 (7.8) Placebo: 321/2,835 (11.1) UFH: 219/6,434 (6.8)	Symptom onset ≤ 24 h for first ≈ 4,300 patients; for patients undergoing primary PCI who received UFH without GP IIb/IIIa inhibitor or neither UFH or GP IIb/IIIa inhibitor, 5 mg IV bolus of fondaparinux followed by 2.5 mg SC; patients without an indication for UFH received placebo control

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	Fondaparinux	Placebo	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
1	470/6,036 (7.8)	321/2,835 (11.1)	0.66 (0.57–0.77)	35 (7)	High

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	Fondaparinux	UFH	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
2	476/6,277 (7.6)	220/3,306 (6.7)	1.15 (0.98–1.36)	9 (6)	High

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). This less impressive difference 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 ACS[196] (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-

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.**
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

Direct thrombin inhibitors have undergone extensive evaluation in acute coronary syndromes, including STE MI patients receiving fibrinolysis (Tables 22, 23). A metaanalysis[199] included individual patient data (n = 9,947) from five trials (≥ 200 patients and ≥ 100 control subjects) evaluating argatroban (n = 1,200),[200] hirudin (n = 8,343),[82,83,201] and bivalirudin (hirulog; n = 404)[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[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[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,[199] the large international HERO-2 trial[67] 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[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.[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)*

Study Year	Patient and ECG Features %	Direct Thrombin Inhibitor Regimen, Dose, Duration	UFH Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Reperfusion Therapy	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Antman et al (TIMI 9A)[79] 1994	Symptom onset ≤ 12 h; STE 100	2.5 mg (initial IV bolus for patients without an indication for UFH) SC daily for up to 8 d or hospital discharge	IV bolus 5,000 U, followed by 1,000 U/h (weight < 80 kg) or 1,300 U/h (weight ≥ 80 kg) for 72–120 h, adjusted to target APTT 60–90 s	Yes	150–325 mg/d	tPA or streptokinase	30	Unknown	Study stopped prematurely due to excessive ICH after 757 patients enrolled
GUSTO IIa Investigators[80] 1994	Symptom onset < 12 h; STE, ST-segment depression or T-wave inversion	Hirudin 0.6 mg/kg IV bolus, followed by 0.2 mg/kg/h infusion for 72–120 h, maintaining APTT < 150 s	IV bolus 5,000 U, followed by 1,000 U/h (weight < 80 kg) or 1,300 U/h (weight ≥ 80 kg) for 72–120 h, adjusted to target APTT 60–90 s	Yes	Yes, dose uncertain	tPA or streptokinase for STE	30	Unknown	Study stopped prematurely due to excessive ICH after 2,564 patients enrolled
Neuhaus et al (HIT-III)[156] 1994	Symptom onset ≤ 6 h; STE 100	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	IV bolus 70 U/kg, followed by 15 U/kg/h infusion for 48–72 h, maintaining APTT 2–3.5 times control	Yes	250 mg initial, 100–500 mg/d	tPA	In-hospital	Hirudin: 13/148 (8.8) UFH: 6/154 (3.9)	Study stopped prematurely due to excessive ICH in the hirudin vs UFH group after 302 patients enrolled
GUSTO IIb Investigators[83] 1996	Symptom onset < 12 h; STE; ST-segment depression or T-wave inversion	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	IV bolus 5,000 U, followed by 1,000 U/h for 72–120 h, adjusted to target APTT 60–85 s	Yes	Yes, dose uncertain	tPA or streptokinase for STE	30	Hirudin: 122/2,075 (5.9) UFH: 127/2,056 (6.2)	Among STE patients only
Antman et al (TIMI 9B)[82] 1996	Symptom onset ≤ 12 h; STE or left BBB	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	IV bolus 5,000 U, followed by 1,000 U/h for 96 h, adjusted to target APTT 55–85 s	Yes	150–325 mg/d	tPA or streptokinase	30	Hirudin: 92/1,511 (6.1) UFH: 76/1,491 (5.1)	
White et al (HERO)[202] 1997	Symptom onset ≤ 12 h; STE 100	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	IV bolus 5,000 U, followed by 1,000 U/h (weight < 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)	Yes	150–325 mg/d	Streptokinase	35	Bivalirudin (hirulog): 14/272 (5.1) UFH: 9/140 (6.4)	If clinically indicated (*eg*, APTT > 120 s or excessive oozing) > 24 h of dosing, infusions reduced by one third; combining low (8/136) and high (6/136) dose bivalirudin (hirulog)

Table 22—*Continued*

Study Year	Patient and ECG Features %	Direct Thrombin Inhibitor Regimen, Dose, Duration	UFH Regimen, Dose, Duration	Blinded	Routine Aspirin Dose	Reperfusion Therapy	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Behar et al (ARGAMI-2)[200] 1998	STE	Argatroban 20 mg/kg IV bolus followed by 2 μg/kg/min infusion or 60 mg/kg IV bolus followed by 4 μg/kg/min infusion for 72 h, target APTT uncertain	IV bolus 5,000 U, followed by 1,000 U/h for 72 h, target APTT uncertain	Yes	Yes, dose uncertain	Streptokinase (50%) or tPA (50%)	30	Unknown	Low-dose argatroban arm discontinued after 199 patients (609 patients in total) due to lack of efficacy
Neuhaus et al (HIT-4)[201] 1999	Age 18–75 yr; symptom onset < 6 h; STE 100	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	IV bolus 70 U/kg, followed by 15 U/kg/h infusion for 48–72 h, maintaining APTT 2–3.5 times control	Yes	300 mg initial, 100–200 mg/d	Streptokinase	30	Lepirduin: 41/603 (6.8) UFH: 39/605 (6.4)	SC injection not given if APTT > 2.5 times control before the 3rd or > 2 times control before the 4th injection; lepirudin discontinued if repeat APTT 12 h after omitting dose > 1.5 times control
HERO-2 Trial Investigators[270] 2001	Symptom onset < 6 h; STE or left BBB	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	IV bolus 5,000 U, followed by 800 U/h (weight < 80 kg) or 1,000 U/h (weight ≥ 80 kg) for ≥ 48 h, adjusted to target APTT of 50–75 s after 12 h	No	150–325 mg/d	Streptokinase	30	Bivalirudin: 919/8,516 (10.8) UFH: 931/8,557 (10.9) OR 0.99 (95% CI 0.90–1.09)	If APTT > 150 s, measured at 18 h with dose reduction if APTT remained > 150 s; after 24 h, dose reduced by one third if major bleeding or APTT > 120 s

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

No. of Studies	No. of Deaths/Patients (%)		Effect		Quality
	Direct Thrombin Inhibitor	UFH	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
6	1,132/13,664 (8.3)	1,117/13,356 (8.4)	0.99 (0.91–1.08)	1 (6)	High

*Includes all randomized trials including patients with STE MI meeting inclusion criteria for the quantitative review by The Direct Thrombin Inhibitor Trialists' Collaborative Group[199] plus the study by the HERO-2 Trial Investigators.[67]

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 trials[218–221] (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 trial[227] 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 24—*Randomized Trials of GP IIb/IIIa Inhibitors vs Control for Patients With Suspected Acute MI: Clinical Description and Results (Section 2.7)*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Kleiman et al (TAMI 8)[218] 1993	Age ≤ 76 yr, symptom onset ≤ 6 h, STE or LBBB with ST segment changes (inferior or anterior)	tPA 100 mg over 3 h (60 mg in the 1st hr with 10% of the dose as an IV bolus, followed by 20 mg for each of the subsequent 2 h)	Abciximab 0.10, 0.15, 0.20, and 0.25 mg/kg IV infusion started 3, 6, and 15 h after start of tPA	No	Aspirin 160–325 mg/d	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 800 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	In-hospital	Abciximab: 1/60 (1.7) Control: 0/10 (0)	All doses combined
Ohman et al (IMPACT-AMI)[219] 1997	Age ≤ 75 yr, symptom onset ≤ 6 h, STE or left BBB with ST-segment changes (inferior or anterior)	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)	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	No	Aspirin 325 mg/d	40 U/kg IV bolus, followed by infusion 15 U/kg/h, adjusted to maintain an APTT of 2–2.5 times control	In-hospital	Eptifibatide: 10/125 (8.0) Control: 4/55 (7.3)	Double-blind for highest dose of eptifibatide for 48 patients; except for patients receiving 108 μg/kg bolus → 0.6 μg/kg/min (n = 18) and initial (n = 21) 135 μg/kg bolus → 0.75 μg/kg/min, where no UFH bolus given and infusion started 60 min after tPA initiation
PARADIGM[220] 1998	Age ≤ 75 yr, symptom onset ≤ 12 h, STE	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	Lamifiban 300 and 400 μg boluses followed by 1.0, 1.5, and 2.0 μg/min infusions for 24 and 48 h	Yes	Aspirin 160–325 mg/d	For tPA: 5,000 U IV bolus, followed by 1,000 U/h for 24 h, to maintain an APTT of 60–85 s; for streptokinase, no UFH in the first 24 h	In-hospital	Lamifiban: 5/236 (2.1) Placebo: 3/117 (2.6)	Except for patients (n = 30) in the first phase of the study
Ronner et al[221] 2000	Symptom onset ≤ 6 h, STE	Streptokinase 1.5×10^6 U over 1 h	Eptifibatide 180 μg/kg IV bolus, followed by 0.75, 1.33, and 2.0 μg/kg/min infusions for 72 h	Yes	Aspirin 250–500 mg, followed by ≥ 80 mg/d	None	30	Eptifibatide: 5/119 (4.2) Placebo: 4/62 (6.5)	

Table 24—*Continued*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Antman et al (TIMI 14)[222] 1999	Age ≤ 75 yr, symptom onset ≤ 12 h, STE	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	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	No	Aspirin 150–325 mg oral or 250–500 mg IV	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 800 U/h); heparin infusions adjusted to target APTT 50–70 s	30	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])
Antman et al (TIMI 14)[223] 2000	Age ≤ 75 yr, symptom onset ≤ 12 h, STE	Reteplase 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 boluses given 30 min apart	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	No	Aspirin 150–325 mg oral or 250–500 mg IV	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 800 U/h) or 30 U/kg IV bolus (maximum 2,000 U), followed by infusion 4 U/kg/h (maximum 400 U/h); heparin infusions adjusted to target APTT 50–70 s	30	Reteplase: 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 + 5 × 10^6 U): 8/92 (8.7)	

Table 24—*Continued*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
SPEED[224] 2000	Symptom onset ≤ 12 h, STE	Reteplase 5, 7.5 or 10 × 10^6 U bolus followed by no bolus or 2.5, 5 or 10 × 10^6 U bolus given 30 min later	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started in emergency department	No	Aspirin 150–325 mg po or 250–500 mg IV, followed by 80–325 mg/d po	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	30	Retplase: 6/109 (5.5) Abciximab alone: 2/63 (3.2) Abciximab + reduced-dose reteplase: 12/356 (3.4)	
Giugliano et al (INTEGRITI)[226] 2003	Age ≤ 75 yr, symptom onset ≤ 6 h, STE	Tenecteplase full-dose (0.53 mg/kg) or reduced-dose (0.27 or 0.40 mg/kg)	Eptifibatide 180 μg/kg IV bolus, followed by 90 μg/kg or 180 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	No	Aspirin 162–325 mg oral or 150–500 mg IV, followed by oral daily	60 U/kg IV bolus (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 800 U/h) for full-dose tenecteplase or 7 U/kg/h (maximum 800 U/h) for low-dose tenecteplase, adjusted to target APTT 1.5–2.5 times control	30	Full-dose tenecteplase: 6/118 (5.1) Reduced-dose tenecteplase + eptifibatide: 15/299 (5.0)	1.0 μg/kg/min infusion for patients with renal dysfunction (creatinine 2–4 mg/dL; n = 5); infusion could be reduced by 33% at investigator's discretion in case of mild bleeding (n = 18)
Brener et al (RAPPORT)[231] 1998	Symptom onset ≤ 12 h, STE or new left BBB	Primary PCI (balloon angioplasty or directional atherectomy); stents allowed for large residual dissections with > 50% stenosis and for abrupt or threatened vessel closure	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%)	Yes	Asprin (dose unknown); ticlopidine in 18% of patients (who received stents)	IV bolus 100 U/kg, followed by additional weight-adjusted doses to maintain an ACT > 300 s during the procedure and up to maximum 48 h, target APTT 60–85 s	30	Abciximab: 6/241 (2.5) Placebo: 5/242 (2.1)	

Table 24—*Continued*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Neumann et al (ISAR-2)[232] 2000	Patients undergoing stent placement ≤ 48 h of STE MI	Fibrinolysis (22%)	Abciximab 0.25 mg/kg IV bolus, followed by 10 μg/min infusion for 12 h started before PCI	No	Asprin 500 mg IV, then 100 mg bid; ticlopidine 250 mg bid	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	30	Abciximab: 4/201 (2.0) Placebo: 8/200 (4.0)	
Montalescot et al (ADMIRAL)[239] 2001	Symptom onset ≤ 12 h, STE	Primary PCI	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)	Yes	Aspirin, dose unknown; ticlopidine 250 mg bid in 92% of patients who received stents	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	30	Abciximab: 5/149 (3.4) Placebo: 10/151 (6.6)	
Stone et al (CADILLAC)[14] 2002	Symptom onset ≤ 12 h, STE or left BBB (88%) or other ECG findings if high-grade angiographic stenosis and associated regional wall motion abnormalities (12%)	Primary PCI (stent [50%] or angioplasty [50%])	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	No	Aspirin 324 mg po or 250 mg IV, then 325 mg/d; ticlopidine 500 mg or clopidogrel 300 mg, then 250 mg bid or 75 mg/d, respectively in patients who received stents	IV to achieve an ACT ≥ 350 s or 200–300 s in patients receiving abciximab	30	Abciximab: 20/1,052 (1.9) Placebo: 24/1,030 (2.3)	
Petronio et al[234] 2002	Symptom onset ≤ 24 h, persistent STE > 1 mm limb leads, > 2 mm precordial leads) > 90 min (mean 8.5 h) before fibrinolysis and IRA stenosis > 60% and TIMI flow grade < 3	tPA (88%) or streptokinase (12%)	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)	Yes	Aspirin 300 mg daily; ticlopidine 250 mg bid for 1 wk followed by 250 mg/d in patients who received stents	IV bolus 70 U/kg, followed by infusion 10 U/kg/h (mean 12.7 ± 7.1 h), target APTT 50–70 s	30	Abciximab: 1/44 (2.3) Placebo: 4/45 (8.9)	

Table 24—*Continued*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Zorman et al[235] 2002	Symptom onset ≤ 12 h, STE	Primary PCI (angioplasty)	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 (33%) or prior to angioplasty (33%)	No	Aspirin 250–500 mg/d	IV bolus 70 U/kg	In-hospital	Abciximab: 4/112 (3.6) Control: 5/51 (9.8)	
Antoniucci et al[236] 2003	Symptom onset ≤ 6 h or 6–24 h if evidence of ongoing ischemia, STE	Primary PCI (stenting)	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started prior to PCI	No	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	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	30	Abciximab: 7/200 (3.5) Control: 8/200 (4.0)	
Petronio et al[237] 2003	Symptom onset ≤ 6 h, STE and IRA occlusion with thrombus	Primary PCI	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started prior to PCI	No	Aspirin 300 mg daily; ticlopidine 250 mg bid for 1 wk followed by 250 mg/d in patients who received stents	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	30	Abciximab: 0/17 Control: 0/14	
ASSENT-3[84] 2001	Symptom onset ≤ 6 h, STE or left BBB	Fibrinolysis, tenecteplase full-dose without abciximab: 30 mg for weight < 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)	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h started prior to fibrinolysis (mean 24 ± 14 min)	No	Aspirin 150–325 mg/d; ticlopidine or clopidogrel in 30% of patients during hospitalization	In patients not receiving abciximab: 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 enoxaparin 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	30	Abciximab: 133/2017 (6.6) Control: 231/4,078 (5.7)	Boluses administered before fibrinolysis; initial APTT sample drawn after 3 h

Table 24—*Continued*

Study Year	Patient and ECG Features	Reperfusion Therapy	GP IIb/IIIa Inhibitor Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	UFH Regimen, Dose, Duration	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Antman et al (ENTIRE-TIMI 23)[181] 2002	Age 21–75 yr; symptom onset ≤ 6 h, STE	Fibrinolysis, tenecteplase full-dose without abciximab: 30 mg for weight < 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)	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	No	Aspirin 160 mg po or 250–500 mg IV followed by 100–325 mg/d	In patients not receiving abciximab: IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 12 U/kg/h (maximum 1,000 U/h) for 36 h, or enoxaparin ± 30 mg IV bolus, then 1 mg/kg SC q12h for ≤ 8 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) for 36 h, adjusted to target APTT 1.5–2.5 times control	30	Abciximab: 8/421 (3.3) Control: 7/242 (2.9)	Boluses administered pre-fibrinolysis; initial APTT sample drawn after 3 h with downward UFH adjustments only in the first 6 h
GUSTO V[227] 2001	Symptom onset ≤ 6 h, STE or new left BBB	Fibrinolysis, reteplase full-dose without abciximab: 10×10^6 U boluses given 30 min apart or half-dose with abciximab	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min (maximum 10 μg/min) infusion for 12 h	No	Aspirin 150–325 mg po or 250–500 mg IV followed by 75–325 mg/d	In patients not receiving abciximab: IV bolus 5,000 U, followed by infusion 1,000 U/h for ≥ 80 kg or 800 U/h for weight < 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	30	Abciximab: 468/8328 (5.6) Control: 488/8,260 (5.9)	

As noted above (Section 2.4), the ASSENT-3 study[84] 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 U/kg bolus [maximum, 3,000 U] followed by 7 U/kg/h [maximum, 800 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 μg/kg [maximum, 10 μg/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% vs 2.2% vs 4.2%, p = 0.0009). Rates of stroke (1.49% vs 1.52%) and ICH (0.94% 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% vs 2.3%, p = 0.0032) were significantly higher with combination treatment,[84] with particularly high rates in patients > 65 years old (*eg*, major bleeding, 7.2% vs 3.1%).[194] 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).[193]

Together with the ENTIRE-TIMI 23 phase II study results,[181] a metaanalysis[230] of these three trials (n = 23,166) [Tables 24, 25] found no difference in those patients receiving abciximab (and half-dose fibrinolysis) compared to no abciximab (and full-dose fibrinolysis) in 30-day mortality (5.8% vs 5.8%; OR, 1.0; 95% CI, 0.9 to 1.12; p = 0.95) or 6- to 12-month mortality (8.6% vs 8.3%; OR, 1.04; 95% CI, 0.95 to 1.15; p = 0.41), despite a reduction in 30-day reinfarction (2.3% vs 3.6%; OR, 0.64; 95% CI, 0.54 to 0.75; p < 0.001). Major bleeding rates were significantly higher in patients receiving abciximab (5.2% vs 3.1%; OR, 1.77; 95% CI, 1.55 to 2.03; 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[230] of eight randomized trials[14,231–237] (n = 3,949) conducted in patients undergoing primary PCI (except for one study[232] with patients after MI undergoing stenting [n = 401], and another study[234] with patients [n = 89] undergoing rescue PCI), abciximab was associated with a significant reduction in 30-day mortality (2.4% vs 3.4%; OR, 0.68; 95% CI, 0.47 to 0.99; p = 0.047) and 6- to 12-month mortality (4.4% vs 6.2%; OR, 0.69; 95% CI, 0.52 to 0.92; 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.[238] Thirty-day reinfarction rates were

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

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

*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 (CADILLAC[14]), 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 (ADMIRAL[239]) 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, 0.85 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 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 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] tenecteplase[245,246]) was used in five of the studies, with half-dose lysis (alteplase[243]) 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 study[243] (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 h[241]; 5,000 U of prealteplase followed by additional 5,000-U boluses before and after angiography vs 10,000 U for primary PCI[242]; 10,000 U for primary PCI[244]; 60 U/kg [maximum, 4,000 U] with tenecteplase vs 70 U/kg for primary PCI[246] 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 group[246]); the LMWHs fraxiparin (SC for 3 days; in addition to the UFH bolus in the primary PCI group)[244] and enoxaparin (30 mg IV bolus)[245] 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 26—*Randomized Trials of Facilitated vs Primary PCI or Fibrinolysis Alone in Suspected Acute MI: Clinical Description and Results (Section 3.1)*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Zorman et al[235] 2002	Symptom onset ≤ 12 h, STE	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	UFH IV bolus 70 U/kg	No	Aspirin 250–500 mg	In-hospital	Early abciximab + pimary PCI: 0/56 (0) Late abciximab + primary PCI: 4/56 (7.1)	All patients received abciximab before PCI, except third group (n = 51) randomized to no abciximab treatment
Lee et al (TIGER-PA)[252] 2003	Symptom onset ≤ 12; STE or LBBB h	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	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	No	Aspirin, dosing unknown; for stents, clopidogrel 300-mg po loading dose, followed by 75 m/d or tirofiban 500-mg po loading dose, followed by 250 mg bid for at least 28 d	30	Early irofiban + primary PCI: 1/50 (2.0) Late tirofiban + primary PCI: 1/50 (2.0)	All patients received tirofiban before PCI
Mesquita Gabriel et al (ERAMI)[250] 2003	Symptom onset < 12 h, STE	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion in the emergency department	UFH IV bolus 5,000 U (77% of patients)	No	Aspirin 250 mg	30	Early abciximab + primary PCI: 4/36 (11.1) Late abciximab + primary PCI: 5/38 (13.2)	All patients received abciximab before PCI
Arntz et al (REOMOBILE)[249] 2003	Age < 80 yr; symptom onset < 6 h; STE	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	UFH 70 U/kg IV bolus	No	Aspirin 500 mg	30	Early abciximab + primary PCI: 0/52 (0) Late abciximab + primary PCI: 1/48 (2.1)	All patients received abciximab before PCI
Cutlip et al[253] 2003	Symptom onset ≤ 12 h; STE	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	UFH regimen at the discretion of the treating physician	No	Regimen at the discretion of the treating physician	30	Early tirofiban + primary PCI: 0/28 (0) Late tirofiban + primary PCI: 1/30 (3.3)	All patients received tirofiban before PCI

Table 26—*Continued*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
van't Hof et al (On-TIME)[251] 2004	Age < 80 yr, female age ≥ 50 yr; symptom onset ≤ 6 h; STE	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	UFH IV bolus 5,000 U	Yes	Aspirin 250 mg IV, then unknown dose daily; clopidogrel 300-mg po loading dose, followed by 75 mg/d for 1 mo	30	Early tirofiban + primary PCI: 9/245 (3.7) Late tirofiban + primary PCI: 2/247 (0.8)	All patients received tirofiban before PCI
Gyongyosi et al (ReoPro-BRIDGING)[217] 2004	Symptom onset ≤ 6 h; STE	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	UFH IV bolus 60 U/kg, followed by an additional bolus to maintain an ACT 200–300 s during the procedure	Yes	Aspirin 250-mg IV bolus, followed by 100 mg/d po; clopidogrel 300-mg oral load, followed by 75 mg/d	30	Early abciximab primary PCI: 0/28 (0) Late abciximab + primary PCI: 0/27 (0)	All patients received abciximab before PCI
Zeymer et al (INTAMI)[254] 2004	Symptom onset, < 12 h; STE or new left BBB	Eptifibatide 180 μg/kg IV boluses (10 min apart), followed by 2.0 μg/kg/min for > 12–24 h in the emergency department or prior to PCI during PCI (optional)	UFH IV bolus 5,000 U, followed by 1,000 U/h infusion, target APTT 50–70 s	No	Aspirin 50-mg IV bolus, followed by unknown dosing; clopidogrel 300-mg po load, followed by 75 mg/d for ≥ 30 d	30	Early eptifibatide + primary PCI: 2/53 (3.8) Late (or no) eptifibatide + primary PCI: 2/49 (4.1)	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
Gibson et al (TITAN-TIMI 34)[256] 2006	Symptom onset ≤ 6 h STE	Eptifibatide 180 μg/kg IV boluses (10 min apart), followed by 2.0 μg/kg/min	UFH IV bolus 60 U/kg (maximum 4,000 U), followed by infusion 7 U/kg/h (maximum 800 U/h)	No	Aspirin 160–325 mg/d po	30	Early eptifibatide + primary PCI: 7/180 (4.0) Late eptifibatide + primary PCI: 5/163 (2.8)	All patients received eptifibatide before PCI

Table 26—*Continued*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Rakowski et al[257] 2007	Symptom onset ≤ 12 h; anterior STE	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion	UFH IV bolus 70 U/kg, with additional boluses to maintain an ACT of 200–250 s	No	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	30	Early abciximab + primary PCI: 0/25 (0) Late abciximab + primary PCI: 0/30 (0)	All patients received abciximab before PCI
Maioli et al[258] 2007	Symptom onset ≤ 12 h; STE	Abciximab 0.25 mg/kg IV bolus, followed by a 0.125 μg/kg/min infusion for 12 h started in the emergency department or after coronary angiography and immediately prior to PCI	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	No	Aspirin 250 mg IV, followed by 100 mg/d po; clopidogrel 300-mg po load, followed by 75 mg/d for ≥ 1 mo	30	Early abciximab + primary PCI: 3/105 (2.9) Late abciximab + primary PCI: 6/105 (5.7)	Includes 55 patients from earlier publication[255] reporting myocardial scintigraphic results; all patients received abciximab before PCI
ASSENT-4 PCI[246] 2006	Symptom onset < 6 h; total STE ≥ 0.6 mV across multiple leads (for inferior MI ≥ 0.4 mV required in leads II, III, and aVF), or new LBBB with concordant STE ≥ 0.1 mV	Tenecteplase full-dose: 30 mg for weight < 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; GP IIb/IIIa inhibitor use at discretion of investigator for primary PCI group (50%) but only in bailout situations in facilitated PCI group (10%)	In patients receiving primary PCI: UFH IV bolus 70 U/kg (no maximum), or in patients receiving facilitated PCI (with full-dose tenecteplase): UFH IV bolus 60 U/kg (maximum 4,000 U); no infusion but additional IV boluses could be administered to obtain an ACT of 350–400 s in the primary PCI group (or 250–300 s if a GP IIb/IIIa inhibitor was used) or 300–350 s in the facilitated PCI group during PCI	No	Aspirin 150–325 mg; clopidogrel 300-mg po load, followed by 75 mg/d	90	Tenecteplase + PCI: 55/823 (6.7) Primary PCI: 41/831 (4.9)	Excluded patients with expected catheter laboratory arrival < 60 min or > 180 min; bailout situations included large residual clot with no or suboptimum recanalization of the IRA

Table 26—*Continued*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
O'Neill et al[241] 1992	Age ≤ 76 h; symptom onset ≤ 4 h; STE	Streptokinase 1.5×10^6 U IV	UFH 10,000 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	Yes	Aspirin 325 mg po	In-hospital	Streptokinase + PCI: 0/58 (0) Primary PCI: 0/63 (0)	
Widimsky et al (PRAGUE)[244] 2000	Symptom onset < 6 h; STE or left BBB	Streptokinase 1.5×10^6 U over 1 h	UFH 5,000 U IV bolus in primary PCI group only; all patients received fraxiparin for 3 d post-MI	No	Aspirin 900 mg IV; ticlopidine 500 mg/d	30	Streptokinase + PCI: 12/100 (12) Primary PCI: 7/101 (6.9)	Excluding 99 patients who had fibrinolysis alone (third treatment group)
Vermeer et al[242] 1999	Age < 80 yr; symptom onset < 6 h; STE or ST-segment depression ≥ 1.5 mV in ≥ 1 lead	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)	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	No	Aspirin 300 mg IV or 160 mg po, followed by 80 mg/d	42	tPA + PCI: 6/74 (8.1) Primary PCI: 5/75 (6.7)	Excluding 75 patients who had fibrinolysis alone (third treatment group)
Ross et al (PACT)[243] 1999	Age ≤ 75 yr; symptom onset ≤ 6 h; STE	tPA 50 mg over 3 min	UFH 5,000 U IV bolus, followed by an infusion of 1,000 U/h (or 1,200 U/h for patients > 80 kg) for 48 h, target APTT 60–85 s	Yes	Aspirin daily, dose unknown	30	tPA + PCI: 11/302 (3.6) Primary PCI: 10/304 (3.3)	

Table 26—*Continued*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Fernandez-Aviles et al (GRACIA-2)[245] 2004	Symptom onset ≤ 12 h; STE	Tenecteplase full-dose: 30 mg for weight < 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	Enoxaparin 30-mg IV bolus for patients receiving tenecteplase	No	Aspirin dosing regimen unknown	30	Tenecteplase + enoxaparin + PCI: 3/104 (2.9) Abciximab + primary PCI: 5/108 (4.6)	
Le May et al (CAPITAL AMI)[248] 2005	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 < 100 mm Hg	Tenecteplase full-dose: 30 mg for weight < 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	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	No	Aspirin 160 mg chewed, followed by 325 mg/d; clopidogrel 300-mg po load, followed by 75 mg/d	30	Tenecteplase: 3/84 (3.6) Tenecteplase + PCI: 2/86 (2.3)	

Table 26—*Continued*

Study Year	Patient and ECG Features	GP IIb/IIIa Inhibitor and/or Fibrinolytic Regimen, Dose, Duration	Heparin Regimen, Dose, Duration	Blinded	Routine Antiplatelet Therapy, Dose	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
ADVANCE MI[260] 2005	Symptom onset ≤ 6 h; STE or new left BBB	Eptifibatide 180 μg/kg IV boluses (10 min apart), followed by 2.0 μg/kg/min; tenecteplase 0.25 mg/kg IV bolus	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)	Yes	Aspirin 162–325 mg po; clopidogrel for stenting	30	Tenecteplase + eptifibatide + PCI: 5/74 (6.8) Eptifibatide + primary PCI: 0/77 (0)	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
Kastrati et al (BRAVE)[259] 2004	Symptom onset < 12 h; STE or new left BBB	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	UFH 60 U/kg (maximum 5,000 U) IV bolus	No	Aspirin 500 mg IV, followed by 100 mg/d po; clopidogrel 75 mg/d for ≥ 6 mo	30	Reteplase + abciximab + PCI: 2/125 (1.6) Abciximab + primary PCI: 2/128 (1.6)	

Table 27—*Facilitated Compared With Primary PCI-Fibrinolytic Therapy, GP IIb/IIIa Inhibitor Therapy, or the Combination Plus PCI vs Primary PCI for Patients With Suspected Acute MI: Summary Evidence Profile (Section 3.1)**

No. of Studies	No. of Deaths†/Patients (%)		Effect		Quality
	Facilitated PCI	Primary PCI	OR (95% CI)	Events Prevented per 1,000 Treated (SD)	
Fibrinolysis					
6	82/1,466 (5.6)	59/1,487 (4.0)	1.43 (1.01–2.02)	16 (8)	High
GP IIb/IIIa inhibitor therapy					
9	17/575 (3.0)	17/573 (3.0)	1.03 (0.49–2.17)	0 (10)	High
Combination (fibrinolysis and GP IIb/IIIa inhibitor) therapy					
2	7/194 (3.6)	2/205 (0.98)	3.07 (0.18–52.0)	26 (15)	High

*Includes all randomized trials meeting inclusion criteria for the quantitative review by Keeley et al.[247]
†Up to 42 days.

Despite significantly better initial pre-PCI and post-PCI rates of TIMI flow grade 3 in two trials,[245,246] 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),[246] 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[246] 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 (*eg*, large residual clot with no, or suboptimum, 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 study[248] not included in the quantitative review[247] 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 (n = 573) with facilitated (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 studies[217,235,249,250,253–255] 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 (58% vs 53%; OR, 1.79; 95% CI, 0.93 to 3.44; p = 0.08). 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 studies,[256,257] and final data in a larger sample of patients[258] from another study previously published.[255] A pilot study[256] 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[255,258] or anterior[257] STE MI resulted in better angiographic and myocardial perfusion (assessed by scintigraphic[255] and STE resolution[257,258]) 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 (n = 205) to facilitated (n = 194) PCI[247] (Tables 26, 27). Half-dose fibrinolysis (reteplase[259] or tenecteplase[260]) with a standard dose of GP IIb/IIIa inhibitor (abciximab[259] or eptifibatide[260]) was compared with standard does of GP IIb/IIIa inhibitor prior to primary PCI. All patients received aspirin (500 mg IV[259] or 162 to 325 mg po[260]) 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/h][260]) or IV enoxaparin (0.4 mg/kg bolus [maximum, 40 mg]).[260]

The primary end point in one trial[259] 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 recruitment;[260] despite improved IRA 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 study[261] 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 primary 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 trials[242,262–265] 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 trial[242] 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 Middlesborough 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 28—*Randomized Trials of Rescue PCI vs Conservative Care or Repeat Fibrinolysis in Acute STE MI: Clinical Description and Results (Section 4.0)***

Study Year	Patient and ECG Features	Fibrinolytic Therapy	Determination of Failure of Fibrinolysis	Antiplatelet Therapy	Antithrombin Therapy	Time to Angiography/ PCI, min	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Belenkie et al[262] 1992	Age < 76 yr; symptom onset ≤ 3 h; STE	Streptokinase tPA	Angiography undertaken immediately after initiation of fibrinolysis; patients with occluded IRA > 3 h after symptom onset	Aspirin 325 mg	IV UFH 5,000 U bolus, followed by infusion to maintain APTT 1.5–2.5 times control until discharge	Unknown	In-hospital	Rescue PCI: 1/16 (6.3) Conservative: 4/12 (33.3)	
Ellis et al (RESCUE)[263] 1994	Age < 80 yr; coronary angiography ≤ 6 h of symptom onset or ≤ 8 h if severe ongoing chest pain; anterior STE MI	Streptokinase tPA; urokinase; for patients randomized to PCI who had received fibrin-specific agent (tPA), additional streptokinase (500,000 U) or urokinase (1×10^6 U) administered; tPA	TIMI flow grade 0–1 in the LAD after IC nitrate administration and ≥ 90 min post-initiation of fibrinolysis	Aspirin 325 mg chewed, followed by 80–325 mg/d	IV or SC (> 10,000 U bid) UFH for ≥ 3 d	Unknown	30	Rescue PCI: 4/78 (5.1) Conservative: 7/73 (9.6)	In patients randomized to conservative management, PCI or coronary artery bypass graft proscribed for 72 h
Vermeer et al[242] 1999	Age < 80 yr; symptom onset < 6 h; STE or ST-segment depression ≥ 1.5 mV in ≥ 1 lead		TIMI 0–1 flow at the angiogram performed 60–120 min post-lytic administration	Aspirin 300 mg IV or 160 mg po, followed by 80 mg/d po	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	From symptom onset to angiography: 240	42	Rescue PCI: 6/74 (8.1) Conservative: 5/75 (6.7)	Excluding 75 patients who primary PCI (third treatment group)

Table 28—*Continued*

Study Year	Patient and ECG Features	Fibrinolytic Therapy	Determination of Failure of Fibrinolysis	Antiplatelet Therapy	Antithrombin Therapy	Time to Angiography/ PCI, min	Duration of Follow-up, d	Mortality, No./Total (%)	Comments
Sutton et al (MERLIN)[264] 2004	Symptom onset ≤ 10 h; STE	Streptokinase (n = 296; 96%); tPA (n = 11; 4%)	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	Aspirin 300 mg, followed by 75 mg/d; other antiplatelet therapies (*eg*, 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	IV UFH for all patients undergoing PCI, target ACT 300 s	From symptom onset to angiography: 327 ± 121; from 60-min ECG to angiography: 85 ± 36	30	Rescue PCI: 15/153 (9.8) Conservative: 17/154 (11.0)	
Gershlick et al (REACT)[265] 2005	Age ≤ 85 yr; symptom onset ≤ 6 h; STE	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	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	Aspirin dosing unknown; GP IIb/IIIa inhibitors at discretion of treating MD	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	From symptom onset to PCI: 414 (25–75 percentiles, 350–505); from fibrinolysis to PCI: 276	180	Rescue PCI: 9/144 (6.2) Conservative: 18/141 (12.8) Repeat fibrinolysis: 18/142 (12.7)	

*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)*

No. of Studies	No. of Deaths*/Patients (%)		Effect		Quality
	Rescue PCI	Alternative Care	OR (95% CI)	Events Prevented per 1,000 Treated, No. (SD)	
Alternative care = conservative care					
3†	10/160 (6.3)	17/168 (10.1)	0.59 (0.26–1.34)	39 (30)	High
2‡	22/294 (7.5)	32/298 (10.7)	0.67 (0.38–1.19)	33 (24)	High
5§	32/462 (6.9)	49/462 (10.6)	0.63 (0.39–1.00)	37 (19)	High
Alternative care = repeat fibrinolysis					
1	9/144 (6.2)	18/142 (12.7)	0.46 (0.20–1.06)	64 (34)	High

*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 treat patients. One-year follow-up[267] 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[265] 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

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Errata

In the June 2008 supplement, in the article by Hirsh et al, "Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:71S–109S), on page 99S, in column one, Recommendation 2.5.2, the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected, and that version should be used.

In the June 2008 supplement, in the article by Goodman et al, "Acute ST-Segment Elevation Myocardial Infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]:708S–775S), on page 710S, in column one, Recommendation 2.5.2 (and on page 739S column one), the text should read "For patients with acute ST-segment elevation myocardial infarction receiving fibronolytic therapy who have preserved renal function (< 2.5 mg/dL [220 μmol/L] in males and < 2.0 mg/dL [175 μmol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A)." The online version has been corrected and that version should be used.

In the June 2008 supplement, in the article by Kearon et al, "Antithrombotic Therapy for Venous Thromboemobolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" (Chest 2008; 133[suppl]: 454S–545S), the conflict of interest disclosures from the authors were inadvertently left out. They are as follows: Dr. Kearon discloses that he has received grant monies from the Canadian Institutes for Health Research and the Heart and Stroke Foundation of Canada. He is also on an advisory committee for GlaxoSmithKline and Boehringer Ingelheim. Dr. Agnelli reveals no real or potential conflicts of interest or commitment. Dr. Goldhaber discloses that he has received grant monies from Mitsubishi, Boehringer Ingelheim, Sanofi-Aventis, Eisai, GlaxoSmithKline, and AstraZeneca. He has also received consultant fees from Sanofi-Aventis, Eisai, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr. Raskob discloses that he has served on the speaker bureau and advisory committees and has received consultant fees from Bayer, BMS, Daiichi-Sankyo, Pfizer, Sanofi-Aventis, Takedo and Boehringer Ingelheim. Dr. Comerotta discloses that he is on the speaker bureaus of Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline and serves on an advisory committee for ConvaTec, and Bacchus Vascular. He is also a shareholder of LeMaitre Vascular.

In the September 2008 supplement by Tarlo et al, "Diagnosis and Management of Work-Related Asthma: American College of Chest Physicians Consensus Statement" (Chest 2008; 134:1S–41S), some of the subheadings are misleading in the print version. The online version has been corrected and should be used. There is no change to the text, but the level of headings shown on pages 7S–9S, 17S, and 31S–32S is more clear in the corrected online edition. Also, on the Table of Contents pages the Endorsements should read "The Canadian Society of Allergy and Clinical Immunology and The Canadian Thoracic Society".

In the July 2008 issue, in the correspondence by BaHammam et al, "Positive Airway Pressure Therapy and Daytime Hypercapnia in Patients With Sleep-Disordered Breathing" (Chest 2008; 134:218–219), the first author's surname was misspelled. It is BaHammam. It has been corrected in the online edition.

Correction

I have come to realize that I neglected to provide as full a potential conflict of interest statement as I could have in my review article, "Update on the Management of COPD" (Chest 2008; 133:1451–1462). I wish to disclose the following: Bartolome R. Celli has been reimbursed by GSK, BI, Pfizer, AZ, Almirall, and Esteve for participating in advisory boards and spoken at different meetings. The division that Dr. Celli heads has been awarded research grants for different medication trials by the same companies and for the discovery of new biomarkers in COPD, and has received grants for the participation in the development of biological lung volume reduction surgery from the company AERIS. Bartolome R. Celli, MD, FCCP, Pulmonary and Critical Care Medicine, Caritas St. Elizabeth's Medical Center, Boston, MA.

Acute ST-Segment Elevation Myocardial Infarction*

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