Reperfusion Strategies for Acute Myocardial Infarction in the Elderly
Benefits and Risks

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Durham, North Carolina; Brindisi, Italy; and Auckland, New Zealand

The optimal reperfusion strategy in elderly patients with ST-segment elevation myocardial infarction (STEMI) remains a topic of debate. This lack of consensus stems from the exclusion or under-representation of the elderly in clinical trials. This review evaluates the available literature pertaining to reperfusion therapy for the treatment of STEMI in the elderly. We identified all published studies evaluating the effectiveness of thrombolytic therapy, primary percutaneous coronary intervention (PCI), or adjunctive therapies to reperfusion by conducting an electronic search of MEDLINE through December 2003. Meta-analysis of clinical trials suggests a survival benefit of thrombolytic therapy in the elderly with STEMI, whereas some observational studies have raised concerns about the lack of short-term benefit or possibility of harm with thrombolysis. However, most observational studies demonstrate improved intermediate-term survival with thrombolysis. In contrast, multiple clinical trials and observational studies indicate improved survival and low risk of stroke with primary PCI compared with thrombolysis in elderly patients with STEMI. Information on the efficacy of newer antithrombotic agents as adjunct to thrombolysis or primary PCI is scarce. Available data suggest an increased risk of intracerebral bleeding with the combination of a fibrin-specific agent and a glycoprotein IIb/IIIa receptor antagonist in patients >75 years of age. Clearly targeted large-scale clinical trials are needed to evaluate the relative merits of available reperfusion strategies as well as newer antithrombotic adjunctive therapies in the elderly with STEMI.

Despite the greater incidence and risk of ST-segment elevation myocardial infarction (STEMI) among older patients (1–3), several large randomized clinical trials evaluating reperfusion therapy for the treatment of these patients (3,4) or the relative merits of mechanical versus chemical reperfusion (5) have systematically excluded elderly patients. Even trials that have included older patients have substantially underrepresented them, with only 10% to 15% of the populations being >75 years of age (4,6–8). Thus, much less is known about the risk/benefits of reperfusion therapy or the optimal reperfusion strategy among the elderly with STEMI. The lack of data regarding reperfusion for STEMI in the elderly, combined with atypical symptoms, high levels of comorbidity, and delayed presentation, have all potentially contributed to the significant underutilization of such treatment in this cohort (2,9,10). Older age is one of the key predictors of failure to use reperfusion therapy in otherwise eligible patients (2,9,10). The proportion of “ideal” elderly patients receiving reperfusion therapy decreases as age increases (64.8%, 65 to 69 years; 60.1%, 70 to 74 years; 50.4%, 75 to 79 years; 35.4%, 80 to 84 years; 20.4%, ≥85 years) (10).

The main objective of this review is to evaluate the available literature pertaining to reperfusion therapy for the treatment of STEMI in the elderly. An extensive electronic search of MEDLINE through December 2003 was conducted in order to identify all published studies evaluating the effectiveness of fibrinolytic therapy, percutaneous coronary intervention (PCI), or adjunctive therapies to reperfusion for treatment of STEMI in the elderly. In addition to reviewing the reference list of each identified study, we examined existing bibliographies of relevant studies and review articles. Finally, we reviewed scientific session abstracts in Circulation, Journal of the American College of Cardiology, and European Heart Journal through December 2003.

INTRAVENOUS THROMBOLYTIC THERAPY IN THE ELDERLY WITH STEMI

Intravenous thrombolysis remains the most common reperfusion strategy for the treatment of patients with STEMI. More recent trials and registries have provided important insights into the risks and benefits of thrombolysis in this high-risk cohort (2,6–9). Randomized clinical thrombolytic trials and registry data show that the risk of intracranial...
hemorrhage increases with age, more so with fibrin-specific agents than with nonspecific agents (6–8,11–12). Despite this increased risk, thrombolysis appears to be beneficial in decreasing mortality in the elderly (3).  

Data from randomized clinical trials. The Fibrinolytic Therapy Trialists’ collaborative group found that younger patients with STEMI have a slightly greater relative reduction in mortality compared with elderly patients, but the higher absolute mortality in the elderly results in higher absolute mortality reduction (3). Thus, a 26% reduction in mortality in patients <55 years of age resulted in 11 lives saved per thousand patients treated in this age group. In contrast, although there was only a 15% reduction in mortality in patients >75 years of age, this resulted in 34 lives saved per thousand patients treated in this age group (Fig. 1) (3,13). Similarly, White et al. (14) examined the effects of age on outcomes in patients enrolled in the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries-I (GUSTO-I) trial and found that the greatest absolute reduction in mortality with thrombolysis occurred in patients 65 to 85 years of age. Furthermore, the net benefit (mortality and/or disabling stroke) was greater with tissue plasminogen activator versus streptokinase. In contrast, the net benefit favored streptokinase among patients >85 years of age. However, because of the small number of patients >85 years of age enrolled in the trial (<1% of the study population), these investigators suggested using caution in making any firm conclusions from this data regarding efficacy of specific fibrinolytic agents among patients in this age group.

Newer thrombolytic agents such as reteplase, teneceplase, and lanoteplase have not been proven to be superior to tissue plasminogen activator in reducing mortality in STEMI patients. However, the Assessment of Safety and Efficacy of a New Thrombolytic (ASSENT) investigators demonstrated that, compared with bolus and infusion of tissue plasminogen activator, the increased fibrin-specific teneceplase was associated with lower rates of major bleeding (15.15% vs. 8.33%) as well as intracranial hemorrhage (3.02% vs. 1.14%) in the high-risk cohort of elderly females >75 years of age and weighing <70 kg (15). In addition, when these investigators compared adjunctive heparin dosing of teneceplase in the ASSENT-2 and -3 trials (doses of which were similar in the two studies), they found that the lower dose of weight-based heparin used in the ASSENT-3 trial was associated with lower major bleeding rates compared with the higher heparin dose used in the ASSENT-2 trial (adjusted odds ratio [OR] 0.49, 95% confidence interval [CI] 0.35 to 0.67), particularly in patients weighing <70 kg (16).

Data from observational registries. Some observational studies have raised concerns about the lack of short-term survival benefit or the possibility of harm with thrombolysis (17–19). Thiemann et al. (17) examined patients from the Cooperative Cardiovascular Project and found that while survival among patients receiving thrombolysis was better in those 65 to 75 years of age, it was significantly lower in those >75 years of age, particularly women. Angeja et al. (18) examined data from the National Registry of Myocardial Infarction-2 and found that, compared with patients receiving no reperfusion therapy, tissue plasminogen activator-treated patients had lower rates of in-hospital death and the composite of in-hospital death or stroke if they were <85 years of age, whereas no such benefit was observed among those ≥85 years of age. Similarly, Soumerai et al. (19) evaluated 2,659 patients ≥65 years of age admitted with STEMI to community hospitals in Minnesota between 1992 and 1996 and found that, compared with no reperfusion, thrombolytic therapy was associated with lower in-hospital mortality in eligible patients <80 years of age, but the odds of death increased 1.4-fold in those ≥80 years of age.

In contrast, other investigations have shown that, although there is no reduction in short-term mortality, intermediate-term mortality is significantly reduced by intravenous thrombolysis in this cohort. A combined analysis from the Maximum Individual Therapy in Acute Myocardial Infarction (MITRA) trial and Myocardial Infarction Registry (MIR) demonstrated that thrombolytic therapy had no impact on in-hospital mortality among patients aged ≥75 years of age, but was associated with a significant reduction in 18-month mortality when compared with no reperfusion (OR 0.58; 95% CI 0.39 to 0.88) (20). Similarly, in an analysis of patients >65 years of age, Berger et al. (21) showed no impact of thrombolysis on 30-day mortality

<table>
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<th>Age</th>
<th>n</th>
<th>30 Day Mortality</th>
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<tr>
<td>&lt; 55</td>
<td>10,047</td>
<td>3.8% 5.4%</td>
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<tr>
<td>55-64</td>
<td>12,252</td>
<td>8.1% 10.7%</td>
</tr>
<tr>
<td>65-74</td>
<td>10,053</td>
<td>15.0% 19.0%</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>3,322</td>
<td>26.0% 29.4%</td>
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<tr>
<td>&gt; 75 (Orig. FTT data)</td>
<td>5,788</td>
<td>24.3% 25.3%</td>
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Figure 1. Benefits of thrombolytic therapy in different age groups. FTT = Fibrinolytic Therapy Trialists.

<table>
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<th>Abbreviations and Acronyms</th>
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<tr>
<td>ASSENT = Assessment of Safety and Efficacy of a New Thrombolytic trial</td>
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<td>CI = confidence interval</td>
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<td>HR = hazard ratio</td>
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<td>MIR = Myocardial Infarction Registry</td>
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<td>MITRA = Maximum Individual Therapy in Acute Myocardial Infarction trial</td>
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<td>OR = odds ratio</td>
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<td>PCI = percutaneous coronary intervention</td>
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<td>RR = relative risk</td>
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<td>STEMI = ST-segment elevation myocardial infarction</td>
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They found that, as compared with thrombolysis, primary PCI may result in lower mortality than thrombolytic therapy in elderly patients with STEMI (Fig. 3) (27–30).

Investigators from the Cooperative Cardiovascular Project evaluated 234,739 patients >65 years of age with STEMI (27). In the eligible cohort, 18,645 (23.2%) received thrombolysis, and 2,038 (2.5%) underwent primary PCI within 6 h of symptom onset. Patients treated with primary PCI had a lower one-year mortality rate (14.4% vs. 17.6%; adjusted HR 0.88; 95% CI 0.73 to 0.94). Among patients without any contraindications for reperfusion, there was a trend toward reduced 30-day mortality with primary PCI (10.1% vs. 12.0%; HR 0.84; 95% CI 0.68 to 1.03).

Primary PCI was also associated with lower rates of reinfarction (4.0% vs. 5.3%; p = 0.009), cerebral hemorrhage (0.2% vs. 1.4%; p < 0.001), and other hemorrhagic end points (21.5% vs. 28.6%; p = 0.001).

The MITRA and MIR investigators did not restrict their analysis to elderly patients with STEMI, but a subgroup analysis of patients ≥65 years of age showed a progressively greater benefit of primary PCI over thrombolytic therapy with increasing age (28). Similarly, in a subgroup analysis of patients with STEMI age ≥75 years enrolled in the National Registry of Myocardial Infarction-2, Tiefenbrunn et al. (29) found a lower rate of combined end point of death and non-fatal stroke favoring primary PCI over alteplase (14.6% vs. 18.4%, p = 0.03). Finally, Mehta et al. (30) analyzed 2,975 patients ≥70 years of age with STEMI enrolled in the Global Registry of Acute Coronary Events.

A recently published very small trial randomly assigned patients aged >75 years with STEMI (n = 47) or intravenous streptokinase (n = 41) and suggested a lower composite of death, reinfarction, or stroke at one year with primary PCI (13% vs. 44%; RR 0.19; 95% CI 0.06 to 0.59) (26). The 30-day (7% vs. 22%; RR 0.25; 95% CI 0.04 to 1.11) and 1-year mortality rates (11% vs. 29%; RR 0.29; 95% CI 0.07 to 1.00) were also lower in the primary PCI group.

**Data from observational studies.** Consistent with the findings of randomized clinical trials, four observational studies have suggested that primary PCI may result in lower mortality than thrombolytic therapy in elderly patients with STEMI (Fig. 3) (27–30).

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**Data from randomized clinical trials.** Many randomized trials have shown more favorable short-term outcomes in STEMI patients with the use of primary PCI rather than with thrombolytic therapy (5). However, these trials did not specifically evaluate elderly patients, thereby limiting the extrapolation of their findings to this cohort. Nevertheless, subset analysis in two trials suggested that primary PCI may be more effective than thrombolytic therapy in elderly patients (23,24). In the Primary Angioplasty in Myocardial Infarction study, 38% of patients enrolled were ≥65 years of age (23). This investigation showed a trend towards fewer deaths (5.7% vs. 15.0%; p = 0.066), lower rate of recurrent ischemia (8.6% vs. 20%; p = 0.048), and a lower composite rate of recurrent myocardial infarction and death (8.6% vs. 27.5%; p = 0.0003) in elderly patients who underwent angioplasty than in those who received thrombolytic therapy. The largest randomized trial, the Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes-IIb (GUSTO-IIb), also showed a trend towards lower 30-day mortality with primary PCI than with thrombolytic therapy among patients ≥70 years of age (24). The Primary Coronary Angioplasty Trialists investigators studied 2,635 patients enrolled in 10 randomized trials of primary angioplasty versus thrombolysis (25).

They found that, as compared with thrombolysis, primary angioplasty was most effective in reducing mortality at 30 days among patients ≥70 years of age than in those <70 years (Fig. 2) (25).
who were eligible for reperfusion therapy. In this eligible cohort, 769 (26.7%) received thrombolysis, whereas 365 (12.7%) underwent primary PCI within 6 h of symptom onset. Patients treated with primary PCI had lower in-hospital mortality (14.4% vs. 17.6%; adjusted OR 0.62; 95% CI 0.39 to 0.96). Primary PCI was also associated with lower rates of reinfarction (1.0% vs. 5.7%; p < 0.003) and a trend toward lower rates of stroke (1.1% vs. 2.8%; p = 0.08). In contrast, there was a trend for higher major bleeding rates in the primary PCI group (8.6% vs. 5.9%; p = 0.09).

**Stenting versus balloon angioplasty during primary PCI.** No randomized clinical trial has evaluated primary coronary angioplasty versus stenting in elderly with STEMI. A subgroup analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial has suggested that stent implantation during primary PCI is more effective in reducing the combined end point of death, recurrent myocardial infarction, disabling stroke, and/or ischemia-driven target vessel revascularization than balloon angioplasty alone in patients ≥65 years of age (OR 0.58; 95% CI 0.38 to 0.85) (31).

**Emergency revascularization versus initial medical stabilization for elderly patients with cardiogenic shock complicating myocardial infarction.** Patients with cardiogenic shock were specifically excluded from almost all randomized trials that compared primary PCI with intravenous thrombolysis and from the analysis of all observational studies evaluating the relative efficacy of the two reperfusion strategies. The SHOCK trial randomly assigned patients with shock due to left ventricular failure complicating myocardial infarction to emergency revascularization, either with PCI or coronary artery bypass grafting (n = 152), or to initial medical stabilization (n = 150) (32). While six-month mortality was lower in the revascularization group than in the medical therapy group (50.3% vs. 63.1%; p = 0.027), this benefit was only observed among patients age <75 years of age, not in those age ≥75 years, raising the question of whether there may be less benefit in the elderly.

In contrast, elderly patients with shock who were clinically selected in the nonrandomized SHOCK registry to undergo revascularization reported marked survival benefit compared with those that underwent late or no revascularization (33). Similarly, two other large registries demonstrated significant survival benefit in patients selected on the basis of physician’s judgment for an invasive strategy (34,35). Thus, elderly with STEMI and shock require individualized consideration for revascularization (1).

**ADJUNCTIVE THERAPIES DURING REPERFUSION IN ELDERLY WITH STEMI**

As with reperfusion therapy, randomized clinical trials provide limited information on the risks and benefits of antithrombin agents (unfractionated or low-molecular-weight heparin or direct thrombin inhibitors [hirudin and its analogues]) or platelet glycoprotein IIb/IIIa receptor antagonists as adjunctive therapies during thrombolysis or mechanical reperfusion in elderly patients with STEMI. Subgroup analyses from some of these trials have provided insight into the merits versus risks of such adjunctive treatments.

**Low-molecular-weight heparins.** While no data are available on the use of low-molecular-weight heparin in elderly patients with STEMI undergoing primary PCI, subgroup analysis in the ASSENT-3 trial suggested similar benefits of low-molecular-weight heparin over weight-adjusted unfractionated heparin in reducing the 30-day composite of death, in-hospital reinfarction, refractory ischemia, intracranial hemorrhage, or major bleeding when given in combination with full-dose tenecteplase in patients with STEMI >75 years of age (Fig. 4) (36). However, in the ASSENT-3 PLUS trial, which compared enoxaparin with weight-
adjusted unfractionated heparin in a prehospital setting, there was an unacceptably high risk of intracranial hemorrhage with enoxaparin in the elderly (2.2% vs. 0.97%; p = 0.047) (37). This may relate to an excessive dose of enoxaparin in the elderly population with decreased creatinine clearance, and underscores the importance of having sufficient data on appropriate doses of low-molecular-weight heparin in elderly populations to specifically evaluate risks and benefits.

**Direct thrombin inhibitors.** Similarly, no data are available on the risks/benefits of direct thrombin inhibitors in elderly patients with STEMI undergoing primary PCI. However, two trials reported the role of direct thrombin inhibitors among the elderly as an adjunct to thrombolysis in subgroup analysis (38,39). Antman et al. (38) compared hirudin with unfractionated heparin as adjunctive therapy to streptokinase or front-loaded tissue plasminogen activator, and suggested no advantage of this direct thrombin inhibitor over unfractionated heparin as an adjunct to thrombolysis in patients ≥65 years of age. Similarly, the Hirulog and Early Reperfusion/Occlusion-2 investigators reported no difference in 30-day mortality in patients ≥65 years of age with STEMI treated with bivalirudin or weight-adjusted unfractionated heparin as adjunct to streptokinase, but noted a trend toward lower in-hospital reinfarction in the bivalirudin-treated patients. However, there was also a trend toward higher intracranial hemorrhage in the patients ≥75 years of age treated with bivalirudin than in those receiving unfractionated heparin (1.0% vs. 0.5%; p = 0.16) (39).

**Glycoprotein IIb/IIIa receptor antagonists.** Data on the safety and efficacy of glycoprotein IIb/IIIa receptor antagonist together with half-dose thrombolytic therapy for patients with STEMI has been reported in subgroup analysis of two large-scale randomized clinical trials (36,40). The ASSENT-3 investigators reported that, in patients >75 years of age, there was a trend towards higher 30-day mortality in patients treated with the combination of tenecteplase and abciximab (22.3%) compared with those treated with tenecteplase and unfractionated heparin (15.9%) or tenecteplase and low-molecular-weight heparin (15.6%) (p = 0.11). Furthermore, the risk for major bleeding complications was threefold higher with full-dose abciximab and half-dose tenecteplase as compared with full-dose tenecteplase (2.6% vs. 0.7%) (Fig. 5) (36). Even though combination therapy had similar 30-day rates of composite of death, in-hospital reinfarction, or refractory ischemia in patients >75 years of age (efficacy end point, OR 1.02; 95% CI 0.76 to 1.36), the composite of efficacy plus safety end point (intracranial hemorrhage or major bleeding) was 30% higher in the combination therapy group (OR 1.30; 95% CI 1.01 to 1.68) (Figs. 4 and 5) (36). The GUSTO-V trial, which compared standard-dose reteplase versus half-dose reteplase with full-dose abciximab in patients with STEMI presenting within 6 h of symptom onset, showed no advantage of combination therapy in reducing the 30-day mortality among patients >75 years of age (18.3% vs. 17.9%; p = 0.83) (40). However, the risk of intracranial hemorrhage in patients >75 years of age was twice as high in the combination group as compared with the full-dose thrombolytic-treated patients (2.1% vs. 1.1%; p = 0.069) (Fig. 5).

In contrast with the increased risk of bleeding (and no difference in mortality) with glycoprotein IIb/IIIa receptor antagonists in combination with thrombolytic therapy (36,40), the subgroup analysis from the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up trial suggested no such increased risk of major bleeding with abciximab when used as an adjunct to stent implantation during primary PCI among patients >65 years of age (41). The 30-day (RR 0.30; 95% CI 0.09 to 0.99) and 6-month (RR 0.35; 95% CI 0.12 to 0.98) composite end points of death, reinfarction, or urgent target vessel revascularization were significantly lower in patients >65 years of age who received abciximab compared with placebo (41). No data exist on the benefits and risk of other glycoprotein IIb/IIIa receptor blockers as adjunct to chemical or mechanical reperfusion in the elderly.

**CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS**

A suggested approach to reperfusion in elderly is shown in Figure 6. The optimal reperfusion strategy in this rapidly growing segment of the population remains to be established in large-scale randomized clinical trials. Until results of such trials are available, current data indicate that, when available, rapid primary PCI (preferably in a high-volume center) is particularly attractive as more elderly are eligible, and it improves reperfusion, reduces recurrent ischemia/infarction, and reduces the risk of intracranial bleeding as compared with thrombolytics in this cohort. In contrast, timely primary PCI is not available at most centers, and the risk of major bleeding (mainly at vascular access sites) is increased with PCI. In addition, the risk of renal failure remains an important concern with primary PCI. While
primary PCI may be considered the reperfusion strategy of choice for elderly patients with STEMI in high-volume hospitals that can achieve rapid time to reperfusion, the proven benefits of thrombolytic therapy should prompt wider use in the elderly in most centers where rapid primary PCI is not available. Efficient systems of transfer may provide the opportunity for wider use of primary PCI, especially for patients with contraindications to thrombolysis.

Based on the studies presented, should all elderly patients with STEMI who present to hospitals where primary PCI is unavailable be transferred immediately to centers that offer it? The inherent time delay in the transfer of patients for primary PCI may offset the relative time-sensitive benefits of reperfusion with this strategy. Rapid initiation of thrombolysis should be considered in these elderly patients in whom timely mechanical reperfusion is not feasible. In no other cohort is the concept of net clinical benefit (mortality benefit weighed against the risk of harm) of thrombolysis more important than in the elderly. Therapy and choice of
agents (fibrin-specific vs. nonspecific agents) should be individualized and based on the risk of mortality and the risk of stroke estimated using published models (1–3,11,12). Preliminary data support the use of weight-based fibrin-specific agent tenecteplase with weight-adjusted heparin as utilized in the ASSENT-3 trials among this age group (36). Current national guidelines for STEMI management designates class III indication to the concomitant use of glycoprotein IIb/IIIa antagonist and low-molecular-weight heparin with fibrinolytic therapy in patients with STEMI >75 years and should be avoided in this age group (1). Reduction in the dose of heparin in older patients, as suggested in the preceding text, and close and early monitoring of anticoagulation activity may be beneficial in reducing the risk of intracranial hemorrhage and major bleeding as well as in improving survival in elderly patients receiving fibrinolysis. Recent trials have reported extremely low rates of intracranial hemorrhage (0.5% to 1.1%) among elderly patients with proper patient selection, weight-adjusted heparin dosing, and close early monitoring of anticoagulation activity (36,37,39).

Decisions regarding transfer after thrombolysis can be based on the clinical course of individual patients. A newer strategy, currently under investigation, is one of facilitated PCI, wherein a patient receives half-dose thrombolytic therapy with full-dose glycoprotein IIb/IIIa inhibitor, followed by rapid transfer to a hospital where PCI can be performed. Studies that have evaluated facilitated PCI have not reported any data on the benefits and risk of this treatment strategy in the elderly (42,43). Given the unacceptable high risk of such combination therapy in the elderly in trials to date, it remains to be established in future trials if the strategy of facilitated PCI would be a good option for the elderly.

Clearly targeted large-scale clinical trials are needed to evaluate the relative merits of the available reperfusion strategies (immediate primary PCI, transfer for primary PCI even when a significant delay is anticipated during transfer, thrombolysis, or facilitated PCI) as well as adjunctive therapies (low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and direct thrombin inhibitors) in the elderly with STEMI. Avoiding selection bias and assuring inclusion of substantial proportions of older patients in most randomized clinical trials may further our understanding regarding the optimal reperfusion strategy in this cohort. Finally, prospective and retrospective registries including the elderly with STEMI are needed to define patterns of care, and may help to refine our understanding of a number of issues that remain unanswered regarding reperfusion in the elderly.

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REFERENCES


