

Angioplasty Strategies in ST-Segment–Elevation Myocardial Infarction

Part I: Primary Percutaneous Coronary Intervention

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Cardiovascular disease is the most common cause of mortality in most developed nations; ≈838 000 in-hospital discharges in the United States in 2005 were for acute myocardial infarction, 29% to 47% of which were acute ST-segment-elevation myocardial infarction (STEMI).¹ The case fatality rate of STEMI has fallen dramatically in the last 3 decades, in part because of the widespread use of reperfusion therapy.^{1–4} STEMI is in most cases due to rupture of an inflamed thin-capped fibroatheroma containing a lipid-rich necrotic core with superimposed secondary thrombosis resulting in coronary artery occlusion.^{5,6} From the seminal demonstration by Reimer et al⁷ that canine coronary occlusion results in a several-hour wave front of necrosis spreading from the subendocardial to the subepicardial myocardium arose the hypothesis that timely restoration of flow in the occluded coronary artery would salvage jeopardized myocardium and enhance survival. Effective reperfusion in STEMI can be achieved by either fibrinolytic therapy or primary percutaneous coronary intervention (PCI) without antecedent fibrinolysis (also generally known as primary angioplasty). Fibrinolysis and PCI also may be combined in a variety of ways, depending on the timing of PCI after fibrinolytic administration, the clinical condition of the patient, and whether PCI is applied routinely or selectively after lytic therapy. Randomized trials have collectively demonstrated enhanced survival and freedom from major adverse cardiovascular events with primary PCI compared with fibrinolysis, and as a result, the expeditious performance of primary PCI has become the preferred reperfusion modality for patients with STEMI presenting at appropriately equipped centers.

The introduction of new devices such as bare metal stents (BMS) and drug-eluting stents (DES) and novel potent antiplatelet and antithrombotic agents have transformed the interventional approach to the patient with STEMI. Important studies have been completed that have addressed previously unsettled issues such as the importance of time to intervention and the utility of late reperfusion. It is thus appropriate and timely to review the data underlying the contemporary interventional approach to STEMI. The first part of this 2-part series will review the essentials of primary PCI in STEMI,

including comparison with fibrinolytic therapy, the impact of PCI-related delays, the evidence for and against delayed infarct artery intervention, the role of BMS and DES, appropriate use of adjunctive antiplatelet and antithrombotic agents, and strategies to expand access to primary PCI, including angioplasty without surgical backup and interhospital transfer. Part 2 reviews interventional strategies after fibrinolytic therapy, discusses volume-quality relationships for PCI outcomes, offers summary recommendations for the patient presenting with STEMI at hospitals with and without interventional facilities, and reviews recent and ongoing investigations to further improve outcomes after catheter-based reperfusion therapy. The conclusions reached rely heavily on the results from randomized controlled trials, with the greatest weight placed on the largest and most contemporary studies. A distinction is drawn in which the evidence-based recommendations in this article differ substantially from the 2004 task force guidelines of the American College of Cardiology (ACC) and American Heart Association,⁸ which recently received a focused update in 2007.⁹ It should be noted, however, that surprisingly few definitive (adequately powered) randomized trials with meaningful (non-composite) clinical end points such as mortality have been performed to address many of these critical issues, often leading to reliance on meta-analysis to guide treatment recommendations. Given the well-known methodological limitations of meta-analysis^{10,11} and recognition that the results of meta-analysis often conflict with more definitive conclusions reached from subsequently performed, appropriately sized randomized trials,¹² caution should be applied in their interpretation, especially when heterogeneity is present or if the results are of borderline significance.

Primary PCI in STEMI

Comparison With Fibrinolytic Therapy

Detailed data are available from 23 prospective controlled trials in which 7739 patients presenting with acute MI (AMI) within 12 hours of symptom onset were randomized to primary PCI or fibrinolytic therapy, including 8 trials of primary PCI versus streptokinase (n=1837) and 15 trials of

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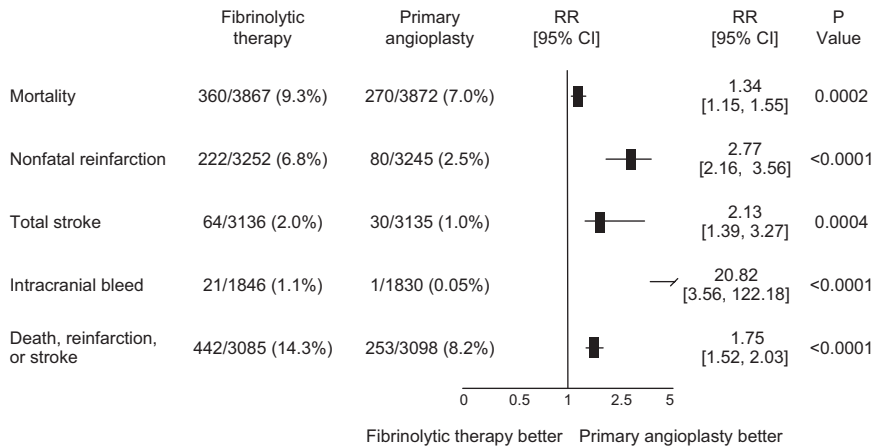


Figure 1. Pooled analysis of the short-term results from 23 randomized trials comparing primary PCI and fibrinolytic therapy in 7739 total patients. Data from Reference 13. Data vary slightly from Reference 13 because of presentation of relative risks (RRs) rather than ORs.

primary PCI versus fibrin-specific agents (n=5902). Primary PCI compared with fibrinolysis resulted in a 25% reduction in death, a 64% reduction in reinfarction, a 95% reduction in intracranial hemorrhage, and a 53% reduction in stroke (Figure 1).¹³ The odds ratios (ORs) for mortality with primary PCI compared with streptokinase and fibrin-specific agents were 0.53 (95% CI, 0.37 to 0.75; $P=0.0005$) and 0.80 (95% CI, 0.66 to 0.96; $P=0.02$). Overall, treatment with primary PCI rather than fibrinolysis saved ≈ 2 lives per 100 patients so treated (even when patients in shock were excluded), similar to the ≈ 2 lives saved per 100 patients treated with fibrinolytic therapy rather than placebo, although major bleeding was increased (7% versus 5%; $P=0.032$).¹⁴ The absolute mortality advantage of primary PCI is greatest in high-risk patients such as those with cardiogenic shock in whom emergency revascularization may save as many as 13 lives per 100 patients treated at 6 months compared with more conservative management.¹⁵ The relative survival benefit of primary PCI may extend to low-risk patients as well, although the absolute reduction in mortality would be proportionately less.¹⁶ Primary PCI also has been shown to salvage more myocardium at risk than fibrin-specific fibrinolytic agents, thus resulting in smaller infarcts.^{17,18} Primary PCI compared with fibrinolysis also reduces recurrent ischemia, resulting in fewer unplanned revascularization proce-

dures and earlier hospital discharge with similar or lower cost.¹⁹

A major mechanism underlying the reduction in mortality and infarct size with primary PCI compared with fibrinolytic reperfusion is the greater rate of successful recanalization of the epicardial infarct-related artery (IRA) with the catheter-based approach. Normal antegrade (Thrombolysis in Myocardial Infarction [TIMI] grade 3) flow in the IRA is restored in $\approx 90\%$ to 95% of patients after primary PCI compared with $\approx 30\%$ to 40% after streptokinase and $\approx 50\%$ to 60% after fibrin-specific agents and strongly correlates with early and late survival (Figure 2).^{19–21} In addition, reinfarction is the second-most-common cause of death after reperfusion therapy in STEMI and may result in infarct extension, life-threatening arrhythmias, and mechanical complications such as rupture of a papillary muscle, the left ventricular septum, or the free wall.^{22,23} By treating the underlying fissured plaque, primary PCI also reduces recurrent ischemia and reinfarction compared with both fibrin-specific and -nonspecific agents.¹³ Moreover, reperfusion injury and hemorrhagic transformation of a bland infarction, which occurs after fibrinolytic therapy but rarely after primary PCI,^{24,25} also may result in increased myonecrosis and the mechanical complications of transmural infarction.²⁶ Finally, despite exclusion of patients at high risk for major bleeding and neurological events in the randomized comparative trials,

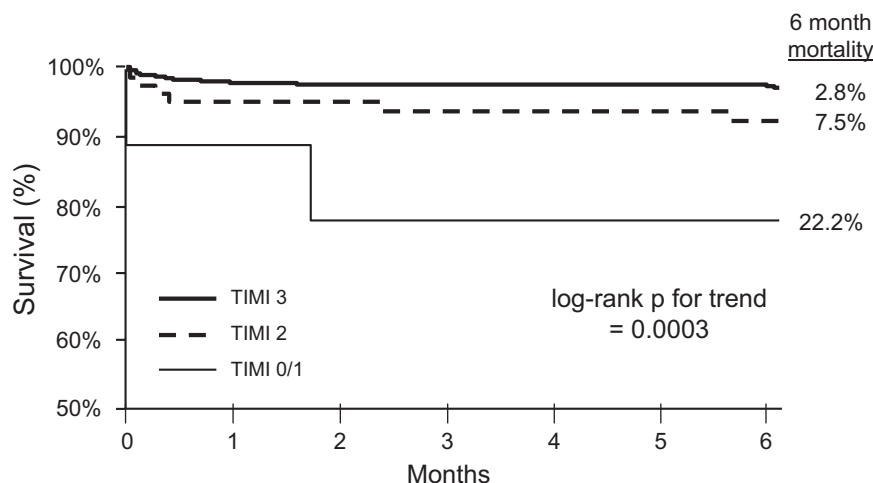


Figure 2. Impact of postprocedure TIMI flow on 6-month survival after primary angioplasty in 2507 patients from the Primary Angioplasty in Myocardial Infarction-1, -2, and stent pilot and randomized trials (unpublished data). Postprocedure TIMI grade 3 flow (present in 92.5% of patients) was strongly correlated with long-term survival. Postprocedure TIMI grade 2 flow (present in 6.0% of patients) was associated with a 3-fold increase in mortality, whereas mortality was increased 8-fold in the 1.5% of patients with postprocedure TIMI grade 0/1 flow.

hemorrhagic stroke occurred in 1.1% of patients after fibrinolysis compared with 0.05% after primary PCI.¹³ Because most patients die or are severely disabled after hemorrhagic stroke in STEMI,^{27,28} avoiding this iatrogenic complication of fibrinolysis contributes to the improved outcomes with primary PCI.

Time Issues in Catheter-Based Reperfusion Therapy

The favorable outcomes achieved with primary PCI in the comparative randomized trials represent the collective results from hundreds of academic and community-based urban and rural hospitals despite variable delays to PCI. Nonetheless, most studies have found that excessive delays to angioplasty impair survival and myocardial recovery after primary PCI. From a pooled analysis of 1199 patients from 4 contemporary primary PCI trials, infarcts measured by technetium-99m sestamibi single-photon-emission computed tomography imaging were smallest when total symptom-to-balloon time was <2 hours, intermediate with 2 to 3 hours of delay, and largest with symptom-to-balloon time >3 hours (median infarct size, 4%, 8%, and 11%, respectively).²⁹ Of note, catheter-based reperfusion within 2 and 3 hours in this series was attained in only 7% and 30% of patients, respectively. Prolonged door-to-balloon^{30–33} or symptom-to-balloon^{34–37} times have been correlated with increased mortality after primary PCI. Registry studies linking PCI delays to adverse outcomes may be confounded by associated patient comorbidities and complications before catheterization that can prolong reperfusion times and other concomitant suboptimal treatment processes, although survivor bias also may play a role in patients recanalized late after symptom onset. Nonetheless, reducing delays from symptom onset to presentation and treatment should improve the prognosis of patients undergoing primary PCI, justifying the current emphasis and resource expenditure toward this goal.

The threshold at which delays to PCI become excessive so that mortality may favor fibrinolysis is unknown. The current ACC/AHA guidelines strongly recommend that all hospital systems achieve a median door-to-balloon time for primary PCI of <90 minutes, with at least 75% of patients treated within 90 minutes of hospital presentation, and that fibrinolytic therapy be administered if longer times to PCI are anticipated.^{8,9} In support of these recommendations are the results of a “meta-regression” analysis in which the incremental delay to PCI compared with fibrinolytic therapy (door-to-balloon minus door-to-needle time) was plotted against the difference in mortality between the 2 reperfusion modalities using 20 summary data points from the randomized comparative trials. This analysis suggested that the survival advantage of primary PCI over fibrinolysis might be lost after a 60-minute incremental delay (consistent with a door-to-balloon time of >90 minutes).³⁸ A limitation of this analysis, however, was that only 1 data point was available to examine PCI-related time delays of >60 minutes, and that study reported lower mortality with primary PCI. In contrast, using institution-based randomized trial data from these same trials from several hundred hospitals, Boersma et al³⁹ determined that the mortality benefit of PCI may persist even with incremental PCI-related delays of up to 2 hours. In that study,

the 30-day mortality among all 6763 randomized patients was 7.9% with fibrinolytic therapy and 5.3% with primary PCI (OR, 0.63). Among the 1349 randomized patients with the greatest incremental PCI delay (>79 to 120 minutes), 30-day mortality was 9.6% with fibrinolytic therapy and 6.6% with primary PCI (OR, 0.62). These findings persisted when only accelerated tissue plasminogen activator trials were considered. Considering time delays from symptom onset to hospital presentation, primary PCI was associated with reduced mortality for all presentation intervals, although the absolute survival benefit of primary PCI compared with fibrinolytic therapy widened in patients with increasing presentation delays, consistent with the fact that older thrombi are more resistant to fibrinolytic reperfusion, whereas primary PCI recanalization rates are independent of time to reperfusion. The reductions in reinfarction and stroke with catheter-based therapy compared with fibrinolytic reperfusion were time independent. These conclusions, however, cannot be considered definitive because subgroup analysis is inherently underpowered and prone to selection bias. Schomig et al⁴⁰ also found that myocardial salvage was greater with primary PCI than fibrinolysis at all time intervals, although more so with greater presentation delays.

The acceptable degree of PCI-related delay appears to depend on the time to presentation and the risk profile of the patient. Subset analysis from the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial of prehospital thrombolysis versus primary PCI suggested that delays to PCI in patients randomized within the first 2 hours of infarct onset might favor the pharmacological approach.⁴¹ Similarly, in the 2082-patient randomized Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, door-to-balloon times were independently correlated with mortality in patients presenting within 2 hours after symptom onset but not later.³⁶ Brodie et al³³ also reported from a large single-center database of 2322 STEMI patients undergoing primary PCI that prolonged door-to-balloon times (>2 versus <2 hours) were associated with higher mortality at 83 months in patients presenting early (<3 hours) (24.7% versus 15.0%; $P<0.0001$) but not late (>3 hours) (21.1% versus 18.5%; $P=0.80$) after symptom onset. In both studies, delays to treatment affected mortality only in high-risk patients (the elderly, patients with anterior infarcts, and patients with heart failure or renal insufficiency).^{33,36} Pinto et al⁴² examined outcomes from 192 509 STEMI patients at 645 hospitals participating in the National Registry of Myocardial Infarction (NORMI) treated with either primary PCI or fibrinolysis. Similar to other studies, the less the incremental PCI-related delay was, the greater the survival advantage of catheter-based reperfusion compared with fibrinolysis was; after multivariate adjustment for baseline differences, mortality remained lower with primary PCI until a PCI-related delay of 114 minutes (which notably applied to only ≈5% of patients). This threshold varied, however, from 179 minutes in patients >65 years of age with nonanterior infarction presenting >2 hours after symptom onset to 40 minutes in patients <65 years of age with anterior infarction presenting within 2 hours of symptom onset.

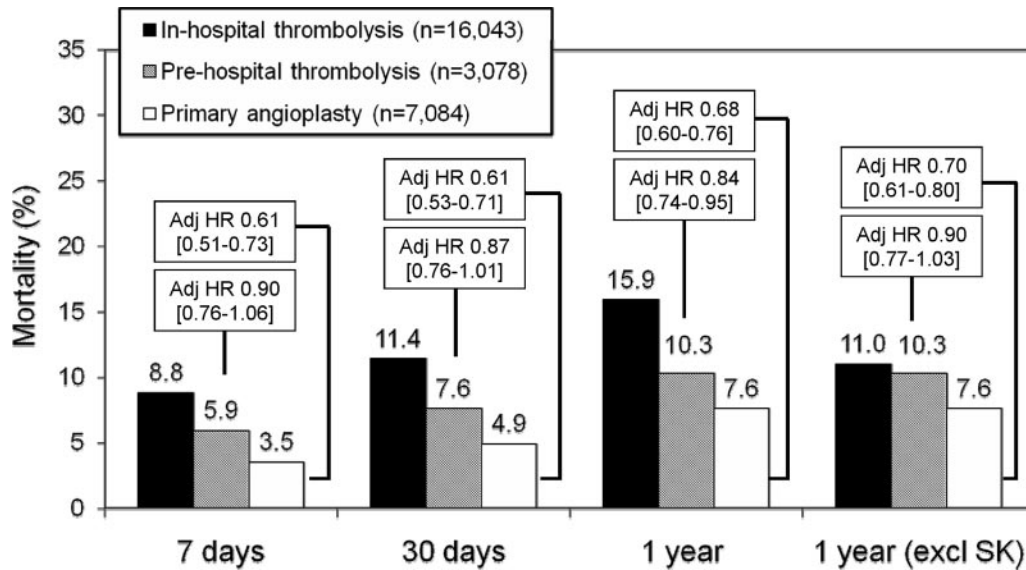


Figure 3. Mortality at different time periods in Sweden between 1999 and 2005 in 26 206 patients with STEMI treated with in-hospital thrombolysis, prehospital thrombolysis, or primary PCI without fibrinolytic therapy. In each case, the adjusted hazard ratio (adj HR; after correction for differences in baseline characteristics and the propensity to receive primary PCI) for patients receiving in-hospital fibrinolysis was set to 1.0. The top box reflects the adjusted HR and 95% CI for the comparison of in-hospital fibrinolysis vs prehospital fibrinolysis; the bottom box reflects the comparison of in-hospital fibrinolysis with primary PCI. Excl SK indicates excluding patients who received streptokinase. Data from Reference 43.

Finally, the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA) investigators reported outcomes from 26 205 consecutive patients with STEMI treated with reperfusion therapy between 1999 and 2005 at 75 hospitals in Sweden.⁴³ The median symptom-to-needle and symptom-to-balloon times were 120 minutes for patients receiving prehospital fibrinolysis (n=3078), 167 minutes for those receiving in-hospital fibrinolysis (n=16 043), and 210 minutes for patients receiving primary PCI (n=7084). Despite these incremental delays to angioplasty, primary PCI was associated with significantly lower early and late mortality than either prehospital or in-hospital fibrinolysis after multivariable adjustment for 24 baseline covariates and treatment propensity (Figure 3). Primary PCI also resulted in significantly lower rates of both early and late reinfarction and reduced hospital length of stay compared with fibrinolytic therapy. The study investigators concluded that the mortality benefits of primary PCI are ≈20% in the early hours after STEMI symptom onset and increase to 30% to 35% in the later hours and that not until a delay to PCI of 6 to 7 hours does the mortality of primary PCI become comparable with fibrinolysis administered within the first hours.⁴³ The conclusions from any observational study must be considered exploratory, given the possibility of unmeasured confounders. Nonetheless, the results from this carefully conducted nationwide registry, in concert with the Boersma et al³⁹ and Pinto et al⁴² analyses, suggest that mortality could be reduced and event-free survival enhanced by withholding fibrinolytic therapy for the preferential performance of primary PCI in most patients.

Late Infarct Artery Intervention

The studies described above refer to PCI performed within 12 hours of symptom onset. Few studies have examined whether

PCI performed later after symptom onset is beneficial. Indeed, reperfusion therapy would be expected to reduce mortality by salvaging myocardium in most cases only if achieved within the first few hours after symptom onset, which is feasible in a minority of patients.⁴⁴ It has been hypothesized that late IRA recanalization of totally occluded coronary arteries might improve survival by preventing infarct expansion, enhancing electrical stability, or providing collateral supply for other ischemic territories, the “open-artery hypothesis.”⁴⁵ PCI of patent but high-grade residual stenoses also may theoretically reduce rates of recurrent ischemia and reinfarction and enhance myocardial recovery.

In the Beyond 12 hours Reperfusion AlternatiVe Evaluation (BRAVE-2) trial, 365 patients with STEMI presenting 12 to 48 hours after symptom onset (mean, 22.5 hours) without ongoing chest pain with both occluded and patent infarct vessels were randomized to either primary PCI or medical therapy.⁴⁶ Infarct size assessed by technetium-99m sestamibi SPECT imaging between 5 and 10 days, the primary end point of the study, was significantly reduced with the invasive compared with the conservative approach (median, 8% versus 13%; $P<0.001$), and myocardial salvage was greater (median, 44% versus 23%; $P<0.001$). This trial, although modest in size and awaiting confirmation, suggests that some patients may have ongoing myocardial injury in the watershed zone or hibernating myocardium late after infarct onset and may benefit from routine PCI within 48 hours of symptom onset.

After a series of small to moderate-sized randomized trials that were inconclusive,^{47–51} the issue of whether occluded infarct vessels should be recanalized days to weeks after STEMI was addressed in the large-scale Occluded Artery Trial (OAT).⁵² In this study, 2166 stable patients with an occluded IRA identified 3 to 28 days after STEMI were prospectively randomized to PCI or conservative therapy.

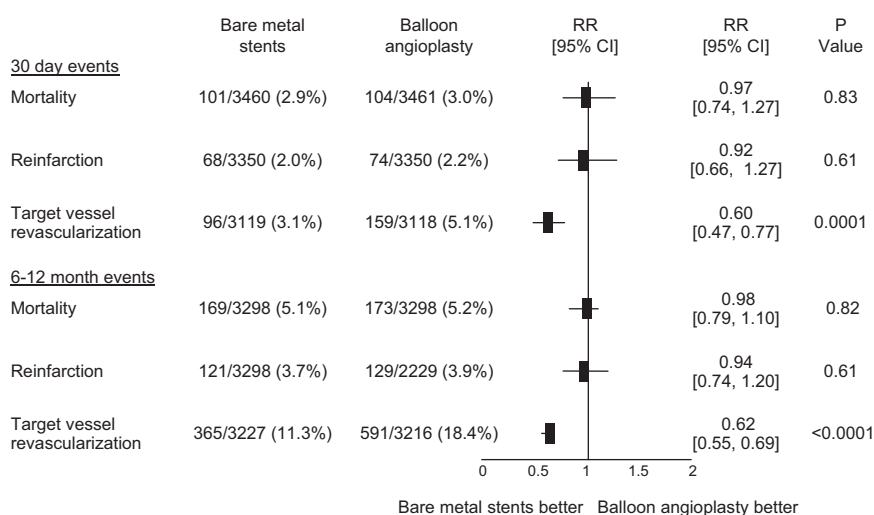


Figure 4. Pooled analysis of the 30-day and 6- to 12-month results from 13 randomized trials comparing BMS with balloon angioplasty alone in 6922 total patients with STEMI. Data from Reference 60. Data vary slightly from Reference 60 because of presentation of relative risks (RRs) rather than ORs.

Stents were implanted in 87% of patients in the invasive arm. At the 4-year follow-up, there were no differences between the 2 groups in either the rate of the primary composite end point of death, reinfarction, or class IV heart failure (17.2% versus 15.6%, respectively; $P=0.20$) or mortality (9.1% versus 9.4%; $P=0.83$). Angina occurred less frequently in the invasive group for the first 2 years after revascularization, resulting in a 19% relative reduction in the need for subsequent revascularization procedures (18.4% versus 22.3%; $P=0.03$), despite the fact that few patients received DES. At the 1-year follow-up angiography (performed in a substudy of 332 patients), left ventricular ejection fraction (LVEF) had increased to the same extent in both groups (mean improvement, 4.2% versus 3.5%, respectively; $P=0.47$), despite the fact that 83% of PCI versus only 25% of medical therapy patients had a patent IRA.⁵³ Of note, only 20% of the patients enrolled in OAT had received prior fibrinolytic therapy, 67% had Q waves consistent with completed transmural infarction, and 90% of the patients who had a stress test before randomization had absent or mild ischemia. The infarct artery was the left anterior descending artery in only 36% of patients, and severe left ventricular dysfunction was uncommon (mean LVEF, 48%). Thus, routine PCI of totally occluded coronary arteries 3 to 28 days after STEMI cannot be recommended in patients without significant ischemia, although further study is required to determine whether the open-artery hypothesis might still apply to patients with larger infarcts, more extensive coronary artery disease, and moderate or severe ischemia.

The importance of ischemia before deferred revascularization was demonstrated in the Swiss Interventional Study on Silent Ischemia Type II (SWISSI-II), in which 201 patients at 3 hospitals with recent STEMI or non-STEMI in whom silent ischemia was confirmed by stress imaging were prospectively randomized to balloon angioplasty (without stents) with intended complete revascularization or optimal medical therapy and were followed up for mean of 10.2 years.⁵⁴ After multivariable adjustment, those treated with the invasive strategy had a 67% reduction in the primary composite end point of cardiac death, nonfatal MI, or symptom-driven revascularization; an 81% reduction in cardiac mortality; a

69% reduction in nonfatal reinfarction; a 52% reduction in symptom-driven revascularization; and improved functional capacity and LVEF at 4 and 10 years (mean LVEF, 54.4% versus 50.6% [$P=0.05$] and 55.6% versus 48.8%, respectively [$P<0.001$]). Limitations of this study include the facts that most patients had well-preserved LVEF and that contemporary PCI modalities and optimal medical therapies were not used. Moreover, as in BRAVE-2, patients enrolled in SWISSI-II had a mixture of both occluded and patent infarct vessels; thus, the results are not directly comparable to OAT. However, as discussed in part 2 of this review, similar benefits of PCI have been demonstrated in patients with ischemia after fibrinolytic therapy.⁵⁵ These studies thus support an approach of routine stress testing after STEMI to identify ischemia with subsequent revascularization when appropriate.

Role of BMS and DES

Although high rates of TIMI grade 3 flow are achieved, dissection and residual luminal narrowing after balloon angioplasty may result in early or late reocclusion or restenosis of the IRA, occurrences that may be prevented by the mechanical scaffolding properties of coronary stents.^{56–59} Thirteen prospective, randomized trials have been performed in which 6922 patients with AMI within 24 hours of onset were randomized to balloon angioplasty or BMS.⁶⁰ Stenting compared with balloon angioplasty resulted in similar rates of early and late mortality and reinfarction, although target vessel revascularization (TVR) was markedly reduced by BMS at both 30 days and 12 months (Figure 4). In the largest such trial, CADILLAC ($n=2082$), BMS and balloon angioplasty resulted in similar rates of postprocedural TIMI grade 3 flow and myocardial recovery at 7 months, underlying the finding of similar survival, although stents resulted in lower rates of restenosis (22.2% versus 40.8%; $P<0.0001$) and IRA reocclusion (5.7% versus 11.3%; $P=0.01$), explaining the dramatically reduced 1-year TVR rates.⁶¹ A 206-patient single-center randomized trial suggested that direct stent implantation, when feasible, may decrease embolization and enhance ST-segment resolution compared with balloon predilatation followed by stent implantation.⁶² A larger trial is warranted to

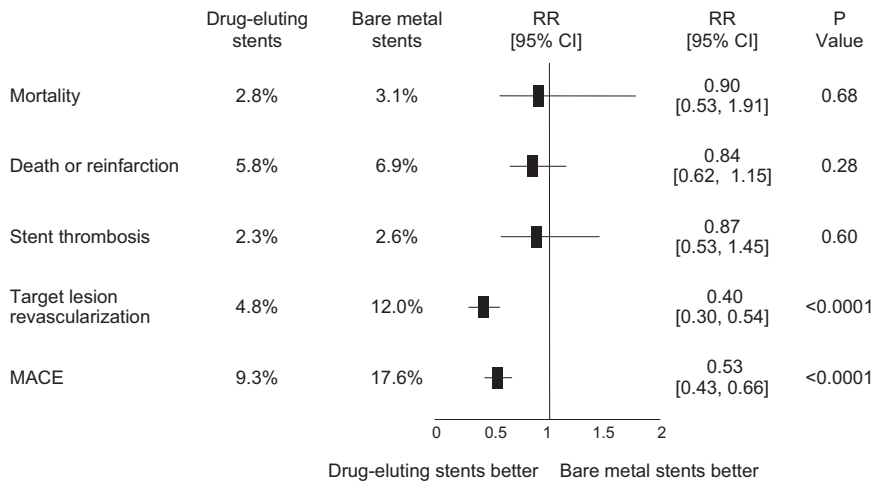


Figure 5. Pooled analysis of 7 randomized trials comparing DES and BMS in 2357 total patients with STEMI. Follow-up rates are at 12 months in 6 trials and 8 months in 1 trial. Mortality data are from 5 trials (1857 patients). MACE indicates major adverse cardiovascular events consisting of death, reinfarction, or TVR (TLR in 1 trial). Data from Reference 64. RR indicates relative risk.

confirm these findings and to determine whether direct stent implantation can further improve event-free survival.

Stents eluting the immunosuppressive and antiproliferative agents sirolimus and paclitaxel reduce restenosis and the need for repeat revascularization procedures compared with BMS in stable coronary artery disease⁶³ and have subsequently been investigated in STEMI. To date, 9 prospective, randomized trials (6 with sirolimus-eluting stents [SES], 2 with paclitaxel-eluting stents [PES], and 1 with multiple DES types) have been reported in which 3728 patients with STEMI within 12 hours of onset were randomized to BMS or DES; the pooled results from 7 of these studies have been reported in a recent meta-analysis.⁶⁴ With follow-up ranging from 8 months to 1 year, DES resulted in a marked reduction in target lesion revascularization (TLR), with similar rates of death, reinfarction, and stent thrombosis (Figure 5). From this analysis, only 13 patients would need to be treated with DES rather than BMS to avoid 1 repeat revascularization procedure. The greater freedom from revascularization with DES may be explained by the further reductions in angiographic restenosis than are achieved with BMS.^{65–68} Of note, although no heterogeneity in efficacy was noted between PES and SES in this meta-analysis,⁶⁴ the reported reduction in TLR with PES compared with BMS in the Paclitaxel-Eluting Stent Versus Conventional Stent in ST-Segment Elevation Myocardial Infarction (PASSION) trial did not reach statistical significance (5.3% versus 7.8%, respectively; $P=0.23$), possibly because of the lack of routine angiographic follow-up resulting in lower-than-anticipated event rates.⁶⁹ However, in a randomized trial of PES versus BMS during primary PCI in which routine follow-up angiography was performed, PES reduced the occurrence of binary restenosis from 24.0% to 1.4% ($P<0.001$).⁶⁸

The 2 largest DES versus BMS trials completed to date in patients with STEMI have recently been reported. In the Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction (DEDICATION) trial, 626 patients with STEMI were randomized to a mixed group of DES (PES, SES, or zotarolimus-eluting stents) or BMS.⁷⁰ At 8 months, patients treated with DES compared with BMS had lower rates of angiographic restenosis (6.7% versus 17.9%; $P<0.001$) and TLR (5.1% versus 13.1%; $P<0.001$), with nonsignificantly

different rates of death (5.1% versus 2.6%; $P=0.14$), reinfarction (1.6% versus 2.6%; $P=0.42$), and stent thrombosis (2.2% versus 2.2%; $P=1.0$). In the Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study (MULTISTRATEGY) trial, 745 patients with STEMI were randomized to SES versus BMS.⁷¹ Angiographic follow-up was not performed in this study. At 8 months, patients treated with DES compared with BMS had lower rates of TVR (3.2% versus 10.2%; $P<0.001$), with nonsignificantly different rates of composite death or reinfarction (5.9% versus 7.5%; $P=0.37$) and stent thrombosis (2.7% versus 4.0%; $P=0.31$).

Before DES can be recommended routinely in STEMI, further studies are required to allay concerns about their long-term safety and efficacy in this setting. In this regard, all of the small to moderate-sized randomized trials performed to date have been underpowered to address low-frequency safety events, which may be increased with DES implantation in STEMI. In a large registry in which 13 500 patients were treated with DES at 17 Spanish hospitals from 2002 to 2006, STEMI was the most powerful determinant of early and late stent thrombosis.⁷² Premature thienopyridine discontinuation is a well-documented risk factor for stent thrombosis,⁷³ a situation that may be both more common and hazardous after STEMI. In the multicenter Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER), 13.6% of 500 patients receiving DES for STEMI were thienopyridine noncompliant at 30 days, a finding associated with markedly higher 1-year mortality (7.5% versus 0.7%; $P<0.0001$).⁷⁴ Finally, Daemen and coworkers⁷⁵ have reported from their sequential experience with different stent types in STEMI that late TVR and adverse cardiac events may be more common with DES than BMS, reducing the relative benefits of DES by 3 years after implantation. Currently, DES implantation in STEMI can be recommended only in selected patients, namely those with lesions at high risk for restenosis without large thrombus burden. The long-term safety and efficacy of DES in STEMI are being addressed in the ongoing Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial in which 3000 patients with STEMI

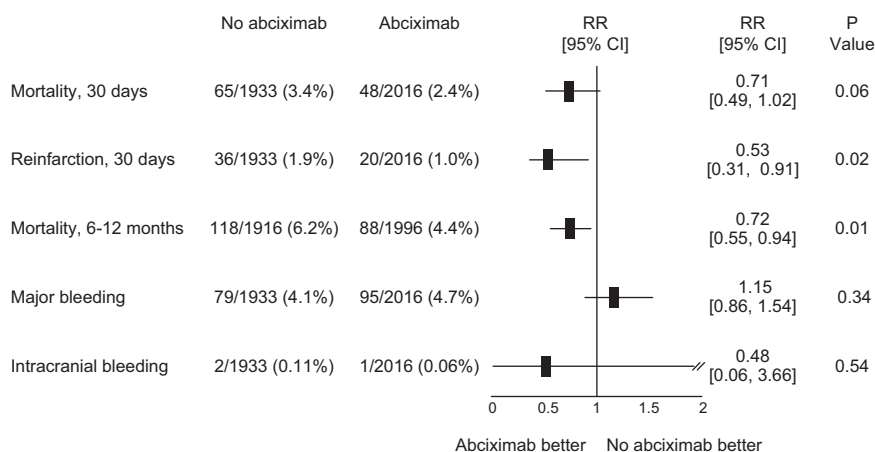


Figure 6. Pooled analysis of 8 randomized trials of primary PCI examining the outcomes of abciximab vs no abciximab in 3949 patients. Data from Reference 87. Data vary slightly from Reference 85 because of presentation of relative risks (RRs) rather than ORs.

undergoing primary PCI have been randomized to PES versus BMS, with follow-up continuing for 5 years.

Adjunctive Antiplatelet and Antithrombin Pharmacology

Aspirin administration reduces mortality in STEMI,⁷⁶ and all patients should receive 324 mg chewed or 250 to 500 mg intravenous aspirin as early as possible to ensure rapid bioavailability. Low-dose aspirin (75 to 162 mg daily) should then be continued indefinitely, which most likely has an efficacy similar to that of higher doses with reduced bleeding complications.^{77,78} Unfortunately, studies to guide thienopyridine administration in primary PCI have not been performed. However, in STEMI patients receiving fibrinolytic therapy (a situation similar to primary PCI in that ADP-induced platelet responsiveness is enhanced),⁷⁹ early treatment with clopidogrel increases TIMI flow, reduces IRA reocclusion, and improves survival.^{80,81} In the Clopidogrel as Adjunctive Reperfusion Therapy: Percutaneous Coronary Intervention Subgroup Study (PCI-CLARITY), PCI was subsequently performed in 1863 of 3491 patients receiving fibrinolysis randomized to a 300-mg clopidogrel loading dose and maintenance therapy versus matching placebo.⁸² The 30-day incidence of cardiovascular death, reinfarction, or stroke after PCI was reduced from 6.2% to 3.6% with clopidogrel treatment ($P=0.008$). Among those patients in whom PCI was performed within 6 hours of randomization, clopidogrel pretreatment reduced composite adverse events from 11.7% to 6.5%. Thus, absent data in the primary PCI setting, administration of a loading dose of clopidogrel as soon as possible before angiography and intervention is recommended. Fewer data are available on which to base selection of the appropriate loading dose. The current ACC/AHA STEMI guidelines recommend a 300-mg clopidogrel loading dose in patients <75 years of age receiving fibrinolytic therapy⁹ without specific recommendations for primary PCI. Before emergent PCI, a 600-mg load may be preferable to 300 mg on the basis of the more rapid onset of action of this higher dose.^{83,84} However, a small (133 patient) randomized trial in patients undergoing primary PCI reported that scintigraphic infarct size was similar after clopidogrel (600-mg loading dose plus 75 mg daily) and ticlopidine

(500-mg loading dose plus 250 mg twice daily), which has a slower onset of action than clopidogrel.⁸⁵

More rapid-acting, investigational P2Y₁₂ inhibitors administered before primary PCI such as cangrelor and prasugrel offer even greater potential for clinical benefit given that the time from drug administration to angioplasty will typically be <60 minutes.⁸⁶ In addition to its more rapid onset of action, prasugrel also effectively inhibits platelet function in patients otherwise hyporesponsive to the effects of clopidogrel.⁸⁷ In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON-TIMI 38) trial, 13 608 patients with acute coronary syndromes (including 3534 with acute or recent STEMI) were randomized to a 300-mg loading dose of clopidogrel or prasugrel started soon before or after PCI, with a maintenance dose continued for 6 to 15 months.⁸⁸ Compared with clopidogrel, prasugrel resulted in a 19% reduction in the primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, outcomes that were consistent in patients with acute or recent STEMI. Hemorrhagic complications occurring with chronic therapy were significantly increased with prasugrel, however, resulting in non-significantly different long-term mortality rates in both groups. Further study is thus warranted to determine whether an abbreviated course of potent, rapid-acting P2Y₁₂ inhibitors (either with or without dose-adjusted chronic therapy) could further improve the prognosis of high-risk patients with STEMI undergoing primary PCI.

Utility of the glycoprotein IIb/IIIa inhibitor abciximab has been evaluated in 3949 patients in 8 prospective randomized trials of patients undergoing primary PCI with balloon angioplasty or BMS.⁸⁹ As shown in Figure 6, the routine addition of abciximab to unfractionated heparin resulted in reduced 30-day rates of mortality and reinfarction and enhanced 6- to 12-month survival without significantly increasing intracranial hemorrhage or major bleeding. In the largest such trial, CADILLAC, in which 2082 patients undergoing primary balloon angioplasty or stenting were randomized to abciximab versus control in a 2×2 factorial design (representing 53% of the patients in the meta-analysis), abciximab resulted in rates of TIMI grade 3 flow similar to control but reduced rates of recurrent ischemia and subacute thrombosis necessitating repeat TVR at 30 days (but

not at 1 year). Abciximab use was associated with slight increases in thrombocytopenia (4.2% versus 1.9%; $P=0.002$) and blood transfusions (5.4% versus 3.4%; $P=0.02$). Myocardial recovery at 7 months and early and late mortality were comparable in both groups.^{61,90} Similarly, in the recently reported BRAVE-3 trial in which 800 patients with STEMI within 24 hours of symptom onset were randomized to primary PCI with or without abciximab, no significant difference in the primary end point of infarct size as measured by technetium-99m sestamibi imaging at 30 days was present between groups (median infarct size, 10% versus 9%; $P=0.76$), nor did clinical outcomes vary significantly except for a modest increase in minor bleeding and thrombocytopenia with abciximab.⁹¹ In contrast, a reduction in in-hospital mortality with abciximab use was reported from a propensity and risk-adjusted analysis among 7321 primary PCI patients from the New York State database.⁹² Differences in patient selection between these studies may account for some of the variance in treatment effect. Regardless, abciximab can be recommended for most patients undergoing primary PCI treated with heparin who are at low risk for bleeding, especially those at high risk for mortality (such as anterior MI) or in whom large thrombus burden is identified. Abciximab should be used in this setting as a 0.25-mg/kg bolus initiated before the first balloon inflation followed by a 12-hour $0.125\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion (10 $\mu\text{g}/\text{min}$ maximum). Insufficient data are available to recommend a provisional strategy of (nonroutine) abciximab use after PCI reserved for angiographic complications⁹³ or a bolus-only approach.

Adequately powered studies to determine whether the cyclic heptapeptide eptifibatide is safe or effective during primary PCI have not been performed,⁹⁴ although this agent is widely used for this purpose. However, in the recently reported Eptifibatide Versus Abciximab in Primary PCI for Acute Myocardial Infarction (EVA-AMI) trial in which 400 patients with STEMI undergoing primary PCI within 12 hours of onset were randomized to abciximab or double-bolus eptifibatide, eptifibatide resulted in similar rates of ST-segment resolution at 60 minutes after the procedure, the primary end point of the study.⁹⁵ Similarly, in the aforementioned MULTISTRATEGY trial,⁷¹ high-dose tirofiban was reported to result in rates of ST-segment resolution and clinical outcomes comparable to abciximab among 745 randomized patients.

Unfractionated heparin is standard of care during primary PCI, with the procedural activated clotting time maintained at 200 to 250 seconds when glycoprotein IIb/IIIa inhibitors are administered. In the last several years, newer antithrombotic agents have emerged that offer theoretical advantages to heparin.⁹⁶ The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT-TIMI 25) trial demonstrated reduced rates of reinfarction with the low-molecular-weight heparin enoxaparin compared with unfractionated heparin in patients receiving fibrinolytic therapy and in those undergoing PCI after fibrinolysis.^{97,98} This agent has not been meaningfully studied in the primary PCI setting, however. The selective factor Xa inhibitor fondaparinux was randomized against unfractionated heparin in 3788 patients undergoing primary PCI in the placebo-controlled, double-blind Organization to Assess Strategies for Ischemic Syndromes (OASIS-6) trial.⁹⁹ Fondaparinux resulted in an

increase in catheter-related thrombus (1.2% versus 0%; $P<0.001$) and angiographic coronary complications (14.3% versus 11.9%; $P=0.04$) with a resultant trend toward increased 30-day rates of death or reinfarction and thus cannot be recommended as the sole anticoagulant during primary PCI.

Compared with heparin plus either abciximab or eptifibatide, the direct thrombin inhibitor bivalirudin has been shown to result in comparable rates of ischemia with reduced major bleeding, minor bleeding, thrombocytopenia, and need for blood transfusions in patients with stable angina, unstable angina, and non-STEMI undergoing PCI.^{100,101} In the recently reported HORIZONS-AMI trial, in which 3602 patients with STEMI undergoing a primary PCI strategy within 12 hours of symptom onset were randomized to unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin alone (with “bailout” glycoprotein IIb/IIIa inhibitors used in 7.2% of patients), treatment with bivalirudin resulted in reduced rates of major bleeding (4.9% versus 8.3%; $P<0.0001$), cardiac mortality (1.8% versus 2.9%; $P=0.028$), all-cause mortality (2.1% versus 3.1%; $P=0.047$), and net adverse clinical events (9.2% versus 12.1%; $P=0.005$).¹⁰² Among 3124 patients in whom stents were successfully implanted, bivalirudin use compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors was associated with an increased rate of acute stent thrombosis (1.3% versus 0.3%; $P=0.0007$) but similar rates of stent thrombosis within 30 days (2.5% versus 1.9%; $P=0.30$) and reduced cardiac mortality among patients undergoing PCI (1.8% versus 2.8%; $P=0.045$).

Expanding Access to Primary Angioplasty

Transfer and No-Surgery-Onsite Strategies

The demonstration that primary PCI compared with fibrinolysis saves lives and otherwise improves cardiovascular outcomes in STEMI has led to recommendations to broaden access to catheter-based reperfusion.¹⁰³ An important limitation of primary PCI, however, is that many patients with STEMI present at hospitals without interventional capabilities. Of the nearly 5000 acute-care hospitals in this country, 2200 have catheterization laboratories, of which only 1200 are capable of performing PCI.¹⁰⁴ In 2005, considering the centers participating in NRMI (reflecting $\approx 60\%$ of US hospitals), $\approx 50\%$ had elective PCI and CABG programs, $\approx 10\%$ performed PCI without open heart surgery facilities, $\approx 20\%$ performed cardiac catheterization without PCI, and $\approx 30\%$ were noninvasive.¹⁰⁵ Two strategies that have thus been proposed to expand the availability of primary PCI are performing angioplasty at centers with catheterization laboratories but without onsite cardiac surgery and transferring patients presenting at noninterventional hospitals to tertiary PCI centers.

Although onsite cardiac surgery is rarely required for emergency complications of primary PCI, $\approx 2\%$ to 5% of STEMI patients undergoing emergent angiography for consideration of angioplasty in whom a patent IRA is found in concert with extensive coronary artery disease are instead triaged to urgent or semielective CABG within several days or weeks,¹⁰⁶ and an occasional patient within 12 hours of symptom onset requires emergency surgery for mechanical complications of STEMI. A coordinated system for rapidly

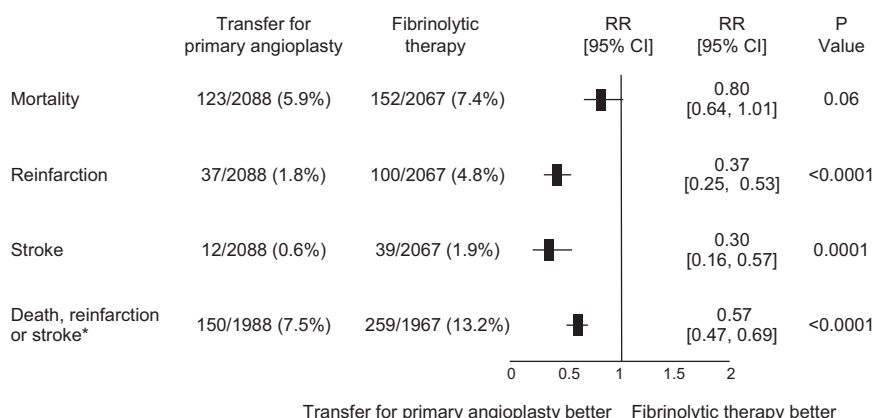


Figure 7. Pooled analysis of 8 prospective trials in which 4155 patients presenting with STEMI at noninvasive centers were randomized to fibrinolytic therapy or ambulance transfer for primary PCI. Some patients were randomized in ambulance. Data from References 113 through 115. RR indicates relative risk. *Data available for 7 of 8 trials.

transferring patients to a surgical center is thus essential if primary PCI at hospitals without onsite surgery is to be considered. Candidate hospitals also must be appropriately equipped and staffed with operators, nurses, and technicians experienced in elective and primary angioplasty. Within this framework, the current ACC/AHA guidelines provide a class IIb recommendation for primary PCI without onsite surgical capabilities, with specific recommendations provided for patient selection and quality control.^{8,9} However, several studies have demonstrated that primary PCI can be performed at US and European centers without onsite cardiac surgery with outcomes comparable to full-service hospitals.^{107–110} Of 52 532 Medicare beneficiaries with STEMI undergoing primary or rescue PCI between 1999 and 2001, 1795 (3.4%) were performed at centers without cardiac surgery. In-hospital mortality was similar after primary PCI or rescue performed at hospitals without versus with onsite cardiac surgery (11.3% versus 12.2% respectively; adjusted OR, 0.93; 95% CI, 0.80 to 1.08; $P=0.34$).¹¹¹ Performance of primary PCI without onsite surgical backup in the United States is an increasingly common practice.¹¹²

Primary PCI at nonsurgical hospitals was evaluated by the Cardiovascular Patient Outcomes Research Team (C-PORT) trial in which 451 patients with STEMI within 12 hours of symptom onset presenting at 11 community hospitals with cardiac catheterization suites but without angioplasty or open heart surgical programs were randomized to accelerated recombinant tissue plasminogen activator or primary PCI after an appropriate training program. Assignment to primary PCI rather than fibrinolysis resulted in a shorter hospital stay (4.5 versus 6.0 days; $P=0.02$) and reductions in the primary composite clinical end point of death, reinfarction, or stroke at 6 weeks (10.7% versus 17.7%; $P=0.03$) and 6 months (12.4% versus 19.9%; $P=0.03$) as a result of significant reductions in reinfarction with trends toward lower mortality and stroke.¹¹³ No patient required emergency CABG for PCI-related complications. Finally, the outcomes of 2208 patients with STEMI undergoing primary PCI at hospitals without onsite surgical facilities were compared with those of 41 681 patients in whom primary PCI was performed at cardiac surgical centers from the National Cardiovascular Data Registry database.¹¹⁴ Reperfusion times were significantly shorter for patients undergoing primary PCI at hospitals without onsite surgery, and the adjusted OR for mortality was nearly identical between the 2 groups (1.02; 95% CI, 0.79 to 1.39;

$P=0.88$). On the basis of these findings, primary PCI may be appropriate at centers without onsite cardiac surgery, although strict quality control measures are required.¹¹⁵

Transferring patients with evolving STEMI from centers without angioplasty to appropriately equipped interventional facilities entails additional delays to reperfusion, although some of this time can be recaptured by avoiding the emergency department at the receiving hospital and other measures.^{103,116} Approximately 80% of the US population lives within 1 hour of a hospital equipped to perform PCI (median distance, 8 miles; median time, 11.4 minutes)¹¹⁷; thus, either an interhospital transfer strategy or, more optimally, prehospital ambulance-based triage to tertiary interventional centers¹¹⁸ could allow most of the country access to primary PCI with acceptable delays. Eight prospective, controlled trials have been performed in which 4155 patients with STEMI presenting at noninvasive hospitals were prospectively randomized to transfer for primary PCI without antecedent fibrinolytic therapy versus onsite fibrinolysis with or without routine or selective transfer for symptoms or ischemia. The reperfusion treatment delays associated with transfer for PCI in these trials ranged from 48 to 103 minutes. Six of these studies were performed between 1997 to 2002 and have been summarized in a previous meta-analysis¹¹⁹; 2 of the trials were completed more recently.^{120,121} Despite the incremental transfer delays, randomization to primary PCI rather than fibrinolysis in these 8 trials significantly reduced the composite end point of death, reinfarction, or stroke by 43%, a difference driven by 67% fewer reinfarctions, 70% fewer strokes, and a strong trend toward a 20% reduction in all-cause mortality (Figure 7).

Despite these favorable outcomes, recent studies have emphasized the fact that transport times for primary PCI in the United States are frequently excessive. Among 4278 patients transferred for primary PCI at 419 hospitals participating in NRM between 1999 to 2002, the median first-door-to-second-door time was 120 minutes, the second-door-to-balloon time was 53 minutes, and the first-door-to-balloon time was 180 minutes; transfer delays correlated with significantly increased mortality.^{122,123} The NRM investigators more recently reported, however, that the median first-door-to-balloon time in the United States has been steadily decreasing (to 143 minutes in 2005), which has been associated with decreasing mortality, so that by 2005 the in-hospital

mortality rates of transfer and nontransfer patients undergoing primary PCI in the United States were similar (3.9% versus 3.8%, respectively).¹⁰⁵

Whether patients presenting at hospitals with cardiac catheterization but without onsite cardiac surgery would be better served by the local performance of primary PCI (the C-PORT approach) or by transfer to a tertiary center with full interventional and surgical facilities has never been directly investigated. However, Wharton et al¹²⁴ reported that appropriately trained physicians could perform primary PCI at select hospitals without onsite surgery with faster times to reperfusion and comparable clinical outcomes compared with those reported from a US-based trial in which patients were transferred for primary PCI at expert tertiary facilities. This approach would be especially preferred if prolonged transfer delays are anticipated.

Summary, Conclusions, and Recommendations

Although primary prevention should be the centerpiece of efforts to reduce the immense burden of cardiovascular disease on society, the prognosis for patients developing STEMI can be markedly improved with timely reperfusion therapy. Unfortunately, approximately one third of patients with STEMI do not receive reperfusion therapy of any kind.^{125,126} In patients undergoing reperfusion therapy, primary PCI compared with fibrinolytic therapy has been shown to save lives and otherwise improve cardiovascular outcomes. The results of primary PCI have continued to improve with advances in technology (stents) and adjunct pharmacotherapy (antiplatelet and antithrombin agents). As a result, primary PCI has emerged as the preferred reperfusion modality when the anticipated incremental delay to intervention is <60 minutes.⁹ However, although delays to intervention are associated with worsened outcomes among patients undergoing angioplasty (and all possible efforts should be undertaken to shorten delays to PCI), recent randomized trials, large-scale registries, and real-world studies suggest that primary PCI compared with the alternative of fibrinolytic therapy improves event-free survival and may reduce mortality in most patients with STEMI even with a several-hour incremental delay to intervention.^{39,42,43} Therefore, absent guidance from a large randomized trial, rather than attempting to identify which individual patients presenting at tertiary centers should be selectively treated with intervention or fibrinolysis on the basis of their baseline demographic features, infarct location, and time from symptom onset, given the well-described relationship between institutional and individual-operator primary PCI volumes and outcomes,^{30,127–130} outcomes may be enhanced by systematically using primary PCI at appropriately equipped and staffed hospitals in all patients except those with contraindications to catheterization or in whom significant delays to angiography are anticipated (with the acceptable door-to-balloon delay conditioned on the delay from symptom onset to presentation and other high-risk patient features). Longitudinal experiences have demonstrated year-to-year reductions in mortality after primary PCI (but not after fibrinolysis) with increasing operator experience.^{43,131} Such institution-wide practices also facilitate implementation of process measures to minimize door-to-balloon times¹³⁰ and other evidence-based recommendations, central to which is appropriate pharmacotherapy. A detailed

algorithm for such decision making is presented in part 2 of this review.

Access to mechanical reperfusion therapy can be expanded further by allowing appropriately trained centers to perform primary PCI without onsite cardiac surgery and instituting “spoke and hub” network systems to systematically transfer patients to primary PCI centers of excellence.^{116,132,133} Similar to the highly successful trauma center model,¹³⁴ patients with STEMI would be best served with emergency medical services involvement to coordinate local or regional ambulance transfer to designated angioplasty centers able to offer primary PCI at all hours with high rates of success and acceptable delays to intervention.¹³⁵ Such programs are being actively developed using prehospital ECGs transmitted to an emergency department or relying on ambulance-based paramedics trained to diagnosis STEMI to determine which patients are transported directly to specialized PCI centers.^{113,133,136} In Ottawa, Canada, an integrated-metropolitan-area approach in which all patients with paramedic-based diagnosis of STEMI were referred to a specialized center for primary PCI resulted in markedly reduced door-to-balloon times compared with interhospital transfer and was associated with reduced mortality compared with the prior period in which fibrinolysis was more widely used.¹³⁷ Moreover, up to 33% of patients with STEMI cannot receive fibrinolysis because of contraindications,¹³⁸ whereas in the Ottawa program, all patients underwent cardiac catheterization, and ≈94% were reperfused by primary PCI.¹³⁷ Given the logistical complexities and costs of establishing a primary PCI program, however, and the political and economic challenges inherent in selectively triaging all STEMI patients to PCI centers of excellence, fibrinolytic therapy will remain the treatment of choice in some healthcare systems, after which selective transfer for immediate or early cardiac catheterization is appropriate. Such combined pharmacoinvasive strategies are discussed in part 2, and detailed recommendations are provided for reperfusion therapy in patients presenting at hospitals with and without interventional facilities.

Disclosures

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