Angioplasty Strategies in ST-Segment–Elevation Myocardial Infarction

Part II: Intervention After Fibrinolytic Therapy, Integrated Treatment Recommendations, and Future Directions

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As reviewed in part I of this report, primary PCI without antecedent fibrinolytic therapy has become widely accepted as the preferred reperfusion modality for patients with ST-segment–elevation myocardial infarction (STEMI) presenting at suitably equipped tertiary facilities. However, primary percutaneous coronary intervention (PCI) is not offered at ≳50% of US hospitals, and many of those that do are unable to offer primary PCI as an around-the-clock service. Primary PCI also is less widely available in many other countries than in the United States. Thus, fibrinolytic therapy continues to be administered to many patients with STEMI.2,3 Given the relatively low rates of successful reperfusion with fibrinolysis,4,5 revascularization often is required afterward, the indications for and outcomes of which are critically evaluated here. The impact of individual operator and institutional volumes on PCI outcomes is reviewed. Evidence-based recommendations for selecting among the various reperfusion therapy options are then offered for the patients with STEMI presenting at centers with and without interventional capabilities, with distinctions drawn where the evidence-based recommendations in this article differ substantially from recently updated task force guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA).5 Finally, recent and ongoing investigations to further improve outcomes after catheter-based reperfusion therapy are summarized.

Angioplasty After Fibrinolytic Therapy

PCI after fibrinolytic therapy in STEMI may be performed in a variety of settings: (1) rescue PCI after failed fibrinolysis in patients with ongoing symptoms, myocardial injury, or persistent coronary occlusion, typically initiated within 60 to 120 minutes after fibrinolytic administration; (2) immediate PCI (also known as facilitated PCI), performed within several hours after fibrinolytic administration, regardless of whether clinical or ECG evidence of ongoing myocardial injury is present; (3) delayed routine PCI, in which patients who are stable for several days after fibrinolytic administration undergo angiography and PCI, regardless of the presence or absence of ischemia or myocardial viability; and (4) delayed selective angioplasty, in which only patients with spontaneous or inducible ischemia after fibrinolysis undergo catheterization and PCI when appropriate.

Similar to primary PCI, each of these interventional strategies describes an approach of angiography followed by triage to angioplasty, coronary artery bypass graft surgery, or medical therapy, a decision based on the coronary anatomy, left ventricular function, and other patient-related factors. However, PCI is performed in ≳80% to 90% of angiographically screened patients requiring revascularization.

Rescue PCI

Rescue PCI refers to the strategy of urgent catheterization after fibrinolytic therapy has clinically failed to restore reperfusion of the infarct artery. Patients in whom fibrinolysis fails to restore patency of the infarct-related artery (IRA) within 90 minutes have worse convalescent left ventricular function, an increased likelihood of developing mechanical complications of transmural infarction, and greater mortality.6,7 Unfortunately, noninvasive methods to reliably detect whether the IRA has recanalized do not exist, perhaps except the infrequent triad of chest pain relief, complete resolution of ST-segment elevation, and reperfusion arrhythmias.8 Theoretically, emergent PCI after clinically failed fibrinolysis might increase coronary patency, halt ongoing myonecrosis, and improve survival. Immediate cardiac catheterization followed by rescue PCI after clinically unsuccessful fibrinolysis has been compared with conservative management in 5 published randomized trials encompassing 920 patients, as recently summarized.9 Stents and glycoprotein IIb/IIIa inhibitors were used in only 2 of these trials.10,11 In the largest such study, the Rapid Early Action for Coronary Treatment (REACT) trial, 427 patients at 35 centers with persistent ST-segment elevation after a variety of fibrinolytic agents were randomized to repeated fibrinolysis, conservative management, or rescue PCI.10 Nonetheless, the primary composite end point of death, reinfarction, stroke, or severe heart failure (HF) within 6 months occurred in significantly fewer patients...
assigned to rescue PCI (13.8% versus 25.6% with repeated fibrinolysis and 22.4% with conservative management; \( P = 0.05 \)) as a result of fewer reinfarctions and trends toward reduced HF and mortality with the invasive approach.

A second contemporary study in 307 randomized patients treated mostly with streptokinase, the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial, reported a reduction in the composite end point of death, reinfarction, stroke, subsequent revascularization, or HF with rescue PCI compared with conservative management (37.3% versus 50%; \( P = 0.02 \)) owing to fewer subsequent revascularization procedures, with trends toward less reinfarction, HF, and mortality.\(^\text{11}\) Stent implantation during rescue PCI has been found to salvage more myocardium than balloon angioplasty\(^\text{12}\); the fact that stents (as well as glycoprotein IIb/IIIa inhibitors) were used less commonly in MERLIN than REACT may partly explain why the benefits of rescue PCI were not quite as robust. Notably, neither trial used thienopyridines, which may further improve outcomes after rescue PCI.

The results of studies evaluating the routine strategy of PCI immediately after fibrinolysis compared with fibrinolysis with more conservative revascularization approaches in the balloon angioplasty era, before the introduction of stents, thienopyridines, glycoprotein IIb/IIIa inhibitors, or even routine aspirin use,\(^\text{16}\) were mixed. Six trials performed nearly 2 decades ago examined the utility of routine immediate balloon angioplasty compared with routine delayed PCI,\(^\text{16–21}\) selective deferred PCI for ischemia,\(^\text{16}\) and/or conservative care.\(^\text{19,20}\) Four trials included patients with an occluded IRA (rescue PCI),\(^\text{16–18,20}\) whereas 2 required a patent IRA.\(^\text{19,21}\) Balloon angioplasty success rates were generally lower when performed immediately after fibrinolysis (65% to 80%) than when performed days to weeks later (85% to 90%). Whereas several of these studies showed improved left ventricular function and/or decreased early rates of recurrent ischemia and reinfarction with immediate PCI,\(^\text{17,19}\) others showed no benefit\(^\text{18,21}\) or increased rates of bleeding, ischemia requiring urgent coronary artery bypass graft surgery, and mortality.\(^\text{16,20}\)

In contrast to these historical studies, 7 contemporary prospective, modest-sized randomized trials have been published and collectively demonstrate that routine PCI with stent implantation in the early hours after fibrinolysis may be beneficial compared with a strategy of delayed routine or ischemia-driven PCI.\(^\text{22–28}\) In the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombosis (PRAGUE) trial, 300 patients within 6 hours of STEMI onset were randomized at hospitals without PCI facilities to streptokinase alone, streptokinase plus transfer for immediate PCI, or transfer for primary PCI alone. Immediate PCI after...
streptokinase compared with streptokinase alone resulted in a trend toward a reduction in the primary 30-day composite end point of death, reinfarction, or stroke (8% versus 15%; \( P=0.12 \)). In the Which Early ST-elevation myocardial infarction therapy (WEST) trial, 304 patients within 6 hours of STEMI onset were randomized before hospital arrival to tenecteplase alone, tenecteplase plus transfer for PCI within 24 hours, or primary PCI.\(^{23} \) PCI after tenecteplase compared with tenecteplase alone resulted in a trend toward a reduction in the 30-day composite end point of death or reinfarction (6.7% versus 13.0%; \( P=0.037 \)) and at 6 months tended to be reduced with immediate PCI compared with fibrinolysis alone (15% versus 25%; \( P=0.10 \)). In the Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL-AMI) trial, 170 STEMI patients treated with tenecteplase within 6 hours of symptom onset were randomized to routine immediate PCI or conservative care with rescue or deferred PCI as clinically indicated.\(^{24} \) The primary composite end point of infarct size assessed by delayed-enhancement magnetic resonance was reduced in the immediate PCI arm (median, 5.2% versus 10.4%; \( P=0.001 \)), and the composite clinical end point of death, reinfarction, major bleeding, or stroke at 6 months tended to be reduced with immediate PCI compared with fibrinolysis alone (15% versus 25%; \( P=0.10 \)).

The results of these 7 published randomized trials with 1996 randomized patients are summarized in Figure 2 in a pooled analysis. The strategy of immediate or early stenting after fibrinolysis compared with ischemia-guided or routine stenting (with early catheterization and revascularization reserved for rescue PCI) in 1996 total patients. Data are at the time of latest follow-up (3 months from the PRAGUE, WEST, CARESS, and Leipzig trials; 6 months from the CAPITAL-AMI and SIAM-III trials; and 1 year from the GRACIA-1 trial).\(^{22-28} \)

### Table 1: Outcomes of Randomized Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Immediate or early PCI with stenting</th>
<th>Delayed ischemia-driven or routine PCI with stenting</th>
<th>RR [95% CI]</th>
<th>RR [95% CI]</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>40/999 (4.4%)</td>
<td>64/997 (7.1%)</td>
<td>0.62 [0.43, 0.91]</td>
<td>0.015</td>
<td></td>
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<tr>
<td>Reinfarction</td>
<td>36/999 (3.6%)</td>
<td>61/997 (6.1%)</td>
<td>0.59 [0.35, 0.88]</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>35/899 (3.9%)</td>
<td>29/898 (3.2%)</td>
<td>1.21 [0.75, 1.95]</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>7/669 (1.0%)</td>
<td>7/665 (1.1%)</td>
<td>0.99 [0.37, 2.70]</td>
<td>0.99</td>
<td></td>
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</table>

Figure 2. Pooled analysis of the results from 7 published randomized trials in patients treated with fibrinolytic therapy comparing the strategy of routine immediate or early catheterization followed by stenting when appropriate and delayed ischemia-guided or routine stenting (with early catheterization and revascularization reserved for rescue PCI) in 1996 total patients. Data are at the time of latest follow-up (3 months from the PRAGUE, WEST, CARESS, and Leipzig trials; 6 months from the CAPITAL-AMI and SIAM-III trials; and 1 year from the GRACIA-1 trial).\(^{22-28} \)
and randomized to urgent transfer to a tertiary center for catheterization and PCI within 6 hours (the “pharmacoinvasive strategy”) or to transfer for elective catheterization within several days unless urgent transfer was required for rescue PCI for failed reperfusion (“standard therapy”).29 PCI was performed in 84% of patients in the pharmacoinvasive arm at a median time of 3 hours after tenecteplase versus in 62% of standard therapy patients at a median time of 27 hours after tenecteplase. Compared with standard therapy, the pharmacoinvasive approach resulted in a significant reduction in the primary 30-day composite endpoint of death, reinfarction, recurrent ischemia, new or worsening HF, or cardiogenic shock (10.6% versus 16.6%; \( P = 0.001 \)), with no significant increases in bleeding end points. The TRANSFER-AMI investigators concluded that transfer to PCI centers should be initiated immediately after fibrinolysis without waiting to see whether reperfusion is successful.

In summary, immediate PCI should be performed if signs of ongoing myocardial injury or ischemia signifying failed thrombolysis are present (rescue PCI). In clinically stable patients, the results of 8 contemporary randomized trials in >3000 patients now strongly support the routine performance of catheterization within hours after fibrinolysis followed by intervention if appropriate. As discussed below, the widespread implementation of such a policy requires a mechanism to routinely transfer patients treated with fibrinolytic therapy to invasive centers. Although the optimal timing for catheterization within the early hours after fibrinolysis has not been delineated, the positive findings of GRACIA-1, in which early systematic PCI within 24 hours of fibrinolysis resulted in favorable outcomes, suggest that a modest delay to catheterization is acceptable, allowing time for transfer of patients receiving fibrinolysis at noninvasive centers.

### Fibrinolysis Before PCI versus Primary PCI Alone

Fibrinolysis before angioplasty may theoretically enhance myocardial salvage by restoring microcirculatory perfusion more rapidly than is possible with primary PCI alone, especially when delays to catheterization are anticipated. Fibrinolysis might also reduce clot burden and, by delineating the infarct lesion, may otherwise facilitate PCI. As such, the strategy of immediate PCI after fibrinolysis has been called facilitated PCI. Several studies have shown that patients undergoing primary PCI have improved survival if the IRA is spontaneously patent before angioplasty.30,31 Whether administering pharmacological agents to induce IRA patency before routine immediate or urgent angioplasty (facilitated PCI) can in a similar fashion improve the prognosis of patients with STEMI has been evaluated in 17 randomized trials enrolling 4504 patients in which primary PCI was compared with angioplasty after the upstream administration of glycoprotein IIb/IIIa inhibitors alone (9 trials, 1148 patients), full-dose fibrinolytic therapy (6 trials, 2957 patients), and reduced-dose fibrinolysis plus glycoprotein IIb/IIIa inhibitors (2 trials, 399 patients). As recently summarized,32 baseline Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow increased from 15% in patients without facilitation to 37% in those receiving upfront pharmacological therapy (\( P = 0.0001 \)), with higher rates achieved with the 2 fibrinolytic regimens than with glycoprotein IIb/IIIa inhibitors (≈42% versus 27%) alone.

Post-PCI TIMI grade 3 flow rates, however, were independent of facilitation (≈89% with facilitation versus ≈88% with control). Contrary to expectations, facilitated PCI compared with primary PCI resulted in a 38% increase in short-term mortality, an 83% increase in reinfarction, a 218% increase in recurrent ischemia necessitating urgent target vessel revascularization, and a 48% increase in major bleeding (Figure 3). Intracranial bleeding and stroke also occurred more commonly with the facilitated strategy. Preprocedural glycoprotein IIb/IIIa inhibitors compared with primary PCI with these agents had no deleterious impact on any of the ischemic end points or mortality and did not increase bleeding rates or stroke, although no benefits were seen either. All of the harmful effects of facilitation were restricted to patients receiving fibrinolytic therapy.32

As recently editorialized, it is understandable in retrospect why facilitated PCI not only failed to improve outcomes compared with primary PCI without antecedent fibrinolysis but also was detrimental.33 Fibrinolytic therapy does not act immediately, requiring ≥60 minutes until a maximal proportion of vessels are recanalized.34 The incremental PCI-related delay in these trials was sufficiently short that lower-than-anticipated TIMI grade 3 flow rates were achieved with

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Facilitated angioplasty</th>
<th>Primary angioplasty</th>
<th>RR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>106/2235 (4.7%)</td>
<td>78/2265 (3.4%)</td>
<td>1.38 [1.04, 1.83]</td>
<td>0.028</td>
</tr>
<tr>
<td>Nonfatal reinfection</td>
<td>74/2190 (3.4%)</td>
<td>41/2223 (1.8%)</td>
<td>1.83 [1.26, 2.67]</td>
<td>0.001</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>66/1725 (3.8%)</td>
<td>21/1745 (1.2%)</td>
<td>3.18 [1.96, 5.15]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major bleed</td>
<td>159/2247 (7.1%)</td>
<td>108/2263 (4.8%)</td>
<td>1.48 [1.17, 1.88]</td>
<td>0.001</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>15/2200 (0.7%)</td>
<td>2/2229 (0.09%)</td>
<td>7.60 [1.94, 29.78]</td>
<td>0.001</td>
</tr>
<tr>
<td>Total stroke</td>
<td>24/2200 (1.1%)</td>
<td>6/2229 (0.3%)</td>
<td>4.05 [1.71, 9.63]</td>
<td>0.0009</td>
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</table>

Figure 3. Pooled analysis of the short-term results from 17 randomized trials comparing facilitated PCI after fibrinolytic therapy and primary PCI without antecedent pharmacological therapy in 4504 patients. Data from Reference 31. Note that the data vary slightly from Reference 31 because of presentation of relative risks (RRs) rather than ORs.
fibrinolysis before PCI. As a result, only an incremental 25% of patients benefited by restoration of TIMI grade 3 flow with fibrinolysis before intervention, although all patients were exposed to the potentially deleterious effects of fibrinolysis and performance of PCI in a lytic state, including increased femoral access site and intracranial bleeding, reperfusion injury, and hemorrhage into the wall of the plaque and myocardium with infarct extension and possibly myocardial rupture.35–37 Fibrinolytic therapy also enhances platelet activation, likely increasing recurrent ischemia and reinfarction. Many patients also presented beyond 2 to 3 hours after infarct onset (the period during which additional myocardium is most likely to be salvaged by early reperfusion), and the amount of myocardium at risk in patients with nonanterior infarction may not have been sufficient to justify the risks of fibrinolysis. However, in the 1667-patient Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention facilitated PCI trial (ASSENT-IV), no signal for benefit was present among patients with anterior infarction, in those randomized early (<2 hours) after symptom onset, or in those with prolonged time from randomization to PCI (>2 hours).40

Finally, in the recently reported Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, 2454 patients with STEMI expected to undergo angiography within 4 hours were randomized to upstream reduced-dose reteplase plus abciximab followed by PCI, to upstream abciximab alone followed by PCI, or to upstream placebo plus primary PCI (with intraprocedural abciximab).41 Door-to-balloon times were 120 minutes in the 60% of patients who were randomized at a hospital with PCI capability and 155 minutes in the 40% of patients who were randomized at a noninvasive hospital and transferred to an interventional center for PCI, representing the longest PCI-related delay times yet tested. There were no significant differences between the 3 arms in the primary 90-day composite end point of all-cause mortality, readmission for HF, resuscitated ventricular fibrillation, or cardiogenic shock (9.8% versus 10.5% versus 10.7%, respectively; P=NS) or mortality (5.2% versus 5.5% versus 4.5%; P=NS), and TIMI major and minor bleeding was increased in the combination reteplase plus abciximab group (14.5% versus 10.1% versus 6.9%; P<0.001). Thus, there currently is no evidence-based justification to routinely pretreat patients in whom primary PCI is intended with fibrinolytic therapy and/or glycoprotein IIb/IIIa inhibitors regardless of the time from symptom onset or anticipated delays to catheterization.

Delayed Routine and Selective Angioplasty

Even when successful, a significant residual stenosis remains in most patients after fibrinolytic therapy, the occurrence of which is associated with high rates of recurrent ischemia and reinfarction.42 Whether routine delayed angioplasty (regardless of the presence of symptoms or ischemia) within days to weeks of fibrinolysis in stable patients would be beneficial was tested in 6 trials in the balloon angioplasty era.43–49 In the largest of these studies, the TIMI-II trial, 3262 patients treated with recombinant tissue plasminogen activator within 4 hours of STEMI onset were randomized to coronary arteriography 18 to 48 hours after fibrinolysis with routine balloon angioplasty if the coronary anatomy was suitable or to angiography and revascularization only in patients with spontaneous or exercise-induced ischemia. The rates of death or reinfarction in the invasive and conservative groups were similar at 42 days (11.1% and 10.1%; P=0.31) and 1 year (14.7% and 15.2%; P=0.83), and no differences were present between groups in rest or exercise ejection fraction either at hospital discharge or at 6 weeks.43,44 Three other trials confirmed these results,45–47 whereas 1 small trial reported improved exercise-induced left ventricular function and less postinfarction angina with routine delayed angioplasty,48 and another showed reduced rates of readmission for severe angina and unplanned revascularization procedures with the invasive approach.49

One reason these early trials of routine delayed angioplasty may have been negative was the enrollment of patients regardless of whether myocardial ischemia and/or viability were present. In the Danish Trial in Acute Myocardial Infarction (DANAMI) trial, 1008 patients with inducible ischemia after fibrinolysis (>99% streptokinase) for a first STEMI were randomized to conservative care or to catheterization followed by revascularization with balloon angioplasty or coronary artery bypass graft surgery when appropriate.50 At a median follow-up of 2.4 years, the invasive approach resulted in lower rates of reinfarction (5.6% versus 10.5%; P=0.004) and readmission for unstable angina (17.9% versus 29.5%; P<0.0001) with similar mortality (3.6% versus 4.4%, respectively). At 4 years, the primary composite end point of death, reinfarction, or readmission for unstable angina occurred in 31.7% of invasively assigned patients versus 44.0% of conservatively managed patients (P<0.0001). Stable angina and antianginal medication use also were significantly reduced with revascularization. Of note, these results were achieved without the use of thienopyridines, glycoprotein IIb/IIIa inhibitors, or stents; thus, the results would most likely be significantly better in the current era.

The results of DANAMI are consistent with the findings from the recently reported Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) in which 201 patients with recent STEMI and silent ischemia confirmed by stress imaging were prospectively randomized to balloon angioplasty or medical therapy. At a mean follow-up of 10.2 years, the primary composite end point of cardiac death, nonfatal MI, or symptom-driven revascularization was reduced by 67% with the invasive strategy; the yearly rate of adverse events was 3.2% with PCI versus 9.5% with conservative management (adjusted hazard ratio, 0.33; 95% CI, 0.20 to 0.55; P<0.001) because of an 81% reduction in cardiac mortality, a 69% reduction in nonfatal reinfarction, and a 52% reduction in symptom-driven revascularization.51 Routine PCI in the postinfarct patient with silent ischemia in this trial also resulted in improved functional capacity and left ventricular ejection fraction at 4 and 10 years, less angina, and reduced use of antianginal medications. In contrast, as discussed in depth in part 1 of this review,1 the routine recanalization of totally occluded coronary arteries 3 to 28 days after STEMI in the absence of ischemia is not benefi-
cational. Thus, catheterization and PCI when appropriate may be recommended for patients in the convalescent phase of STEMI after fibrinolysis if spontaneous or inducible ischemia is present. As described above, however, contemporary data suggest that the optimal approach for the postlytic patient is the systematic practice of routine immediate (<24 hours) angiography followed by PCI when appropriate. A more conservative strategy of stress testing to risk stratify patients may be suitable for hospital systems without ready access to interventional facilities.

**Clinical Recommendations for Patients With STEMI**

As reviewed in this 2-part document, contemporary studies have shown that primary PCI is superior to immediate/facilitated PCI after fibrinolysis and that immediate/facilitated PCI after fibrinolysis (with or without rescue) is superior to fibrinolysis followed by conservative care. As such, efforts to widely implement greater access to intervention are justified. Moreover, as previously discussed, primary PCI may be performed with excellent outcomes at hospitals without onsite cardiac surgery. Randomized trials also have shown improved outcomes for STEMI patients presenting at noninterventional facilities who are transferred for primary PCI rather than administered fibrinolytic therapy. Although the current ACC/AHA guidelines recommend that fibrinolytic therapy be administered rather than primary PCI unless delivered within 2 hours of symptom onset in areas with >4 hours of transportation time to a PCI procedure. Even if the mortality benefit of primary PCI is diminished by delays to reperfusion so that the survival rates with the 2 reperfusion modalities are similar, all patients may still benefit from the primary PCI approach through decreased rates of recurrent ischemia and reinfarction, intracranial bleeding and stroke, and more rapid discharge, considerations that often are ignored when recommendations are made for the selection of reperfusion modality.

A contemporary evidence-based algorithm for management of patients with STEMI based on the collective studies discussed in this 2-part document appears in Figure 4. It should be stressed that this proposed treatment pathway represents solely the author’s evidence-based interpretation of the literature supported by the collective results from large-scale contemporary studies of PCI with and without antecedent fibrinolysis that increased patient access to interventional reperfusion therapy will improve patient outcomes. Patients presenting within 12 hours of symptom onset at appropriately equipped and staffed interventional hospitals should undergo immediate left ventriculography and coronary arteriography followed by PCI if appropriate (typically ~90% of patients). Although the current ACC/AHA guidelines provide a class IIb recommendation for PCI in the setting of STEMI without onsite surgery, as discussed in the first part of this review, excellent results can be obtained at nonsurgical facilities, although minimum volume standards, quality oversight, and a coordinated transfer strategy to hospitals with open heart surgery are mandatory. For patients presenting at noninvasive hospitals capable of transfer for primary PCI with an anticipated first-door-to-balloon time of <2 hours, fibrinolytic therapy may be withheld and transport initiated after administration of aspirin, clopidogrel, and unfractionated heparin. Transport for primary PCI also may be considered despite longer anticipated transfer times if the infarct has been ongoing for several hours, especially for patients with nonanterior infarction or increased bleeding risk after fibrinolysis. Patients presenting within 2 hours of symptom onset with excessive transfer delays should be
treated with fibrinolytic therapy. However, given the demonstration that rescue PCI reduces death and reinfarction, immediate transfer should still be performed, especially in high-risk patients such as those with anterior infarction, left bundle-branch block, or Killip class >1. Finally, given the results of studies demonstrating benefit of systematic catheterization and stenting when appropriate within 24 hours after fibrinolysis, strong consideration should be given to a routine same-day transfer strategy for all patients treated with fibrinolytic therapy, especially if high risk. Stable patients presenting with STEMI 12 to 48 hours after symptom onset should not receive fibrinolysis56 but still may benefit by urgent catheterization and revascularization.57 Thus, transfer also should be considered for patients presenting late at noninterventional facilities. Of course, immediate transfer for primary PCI should be performed for all patients within 12 hours of STEMI onset with strict contraindications to fibrinolysis. Finally, for patients in the convalescent phase of STEMI who did not undergo earlier cardiac catheterization, routine stress testing is recommended, and those with spontaneous or inducible ischemia or severely depressed left ventricular function or HF should undergo catheterization and revascularization if appropriate. No studies have addressed whether stable patients without ischemia and with well-preserved left ventricular function should undergo routine cardiac catheterization >72 hours after MI if treated with fibrinolytic therapy, although IRA recanalization of an occluded vessel identified 3 to 28 days after STEMI cannot be recommended in the absence of ischemia.52

As discussed below, system-wide implementation of interventional strategies in STEMI is likely to reduce mortality further by increasing institutional and operator experience (volume) and facilitating quality improvement programs to further reduce door-to-balloon times and to ensure delivery of evidence-based recommended medications and secondary preventive measures. 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.58 Nonetheless, roadblocks to routine transfer of STEMI patients are considerable and, as recently summarized,59 include the lack of ambulance-based ECGs,60 the mandate in many states to deliver patients to the nearest hospital regardless of expertise or interventional capability, financial disincentives to transfer, lack of adequate staffing and beds at tertiary hospitals that often requires diversion of STEMI patients, and other logistical impediments that to date have resulted in excessively long transfer times in the United States.61 Public policy changes are necessary to increase timely access to primary PCI, and economic implications must be considered.62 Nonetheless, several regional spoke-and-hub systems have already been implemented in which patients presenting at community hospitals without interventional facilities are routinely transferred to a single tertiary hospital for primary PCI. As recently reported, this approach has resulted in significant reductions in door-to-balloon times and excellent clinical outcomes.63–65 Of note, in several of these networks, either all patients63 or those within 3 hours of symptom onset64 presenting at the outer rim are administered fibrinolytic therapy before long-distance transfer to the PCI facility, despite the fact that facilitated PCI has not shown benefit (and in fact has been harmful) in patients with shorter delays to reperfusion. Although the results reported to date in these registries have been favorable,65,66 appropriately powered randomized trials are required to determine whether these approaches are superior to immediate transport without fibrinolysis.

**Strategies to Further Improve Outcomes After Reperfusion Therapy**

**The Importance of Volume and Quality of Care**

With the shift of resources toward intervention in STEMI comes the responsibility to optimize outcomes of catheter-based reperfusion therapy. Numerous studies have demonstrated a strong relationship between the annual number of primary PCI procedures performed and survival on both an institutional and individual operator level. In a report from the National Registry of Myocardial Infarction (NRMI), among >27 000 patients, the multivariate-adjusted odds ratio (OR) for mortality was reduced by 14% and 33% at hospitals performing 1 to 3 and >3 primary angioplasty procedures per month compared with those performing <1 procedure per month.66 No such relationship was found to exist as a function of the number of STEMI patients treated with fibrinolysis.67 In the NRMI-2 and NRMI-3 registries, in-hospital mortality was lower after primary PCI compared with fibrinolysis at hospitals with intermediate (4.5% versus 5.9%, respectively; P<0.001) and high (3.4% versus 5.4%; P<0.001) primary PCI volumes but not at low-volume hospitals (6.2% versus 5.9%; P=0.58).68 Moreover, both door-to-balloon times and mortality have been shown to decrease as the proportion of STEMI patients treated with primary PCI rather than fibrinolysis increases.69 Similarly, between 1994 and 1998 in Germany70 and between 1999 and 2004 in Sweden,44 mortality rates significantly and steadily decreased in patients treated with primary PCI (but not with fibrinolytic therapy), further evidence of the importance of consistency and volume when logistically complex treatment pathways and operator expertise are required such as with primary PCI. Finally, the number of annual procedures performed by individual physicians also has been found to strongly affect in-hospital survival after primary PCI independently of the effect of institutional volume measures.71

The improvement in survival rates with increasing institutional and physician primary PCI volumes may be due in part to parallel decreases in door-to-balloon times, increasing operator expertise, and improvement in other quality-of-care processes. In a recent study of 365 hospitals, 6 hospital practices were independently associated with reduced door-to-balloon times: activating the catheterization laboratory by emergency medicine physicians, via a central page operator, while the patient is en route to the hospital; requiring catheterization laboratory staff arrival within 20 minutes of being paged; having an attending cardiologist always on site;
and using real-time data feedback. Median door-to-balloon times were 31 minutes shorter in hospitals using 4 of these measures compared with none. Commitment to explicit goals to reduce door-to-balloon times, in concert with hospital support and implementation of quality-control measures using regular data feedback, has resulted in significant reductions in door-to-balloon times at individual hospitals.

**Novel Pharmacological Approaches**

Despite universally positive results in murine, canine, and porcine models, most attempts to decrease infarct size in humans beyond that achieved with balloon angioplasty alone have been disappointing. As previously described, glycoprotein IIb/IIa inhibitors have not been convincingly demonstrated to enhance myocardial salvage after primary PCI.

Numerous promising adjunctive pharmacological agents designed to inhibit inflammation, prevent reperfusion injury, optimize myocardial metabolism, improve oxygen delivery, restore intramyocardial hemodynamics, or antagonize adverse neurohumoral mediators active in STEMI have failed to improve the prognosis of patients undergoing primary and rescue PCI. Unsuccessful approaches have included anti-neutrophil antibodies, poloxamer-188 and fluosol, magnesium, Na⁺/H⁺ exchange inhibitors, trimetazidine, superoxide dismutase and other antioxidants or free radical scavengers, glucose-insulin-potassium, intracellular calcium modulation, magnesium, and most recently inhibitors of vascular endothelial growth factor, complement, and nitric oxide synthase.

In contrast to these experiences, adenosine as an adjunct to reperfusion therapy in STEMI has shown potential to enhance myocardial salvage. Adenosine displays antiinflammatory and antiplatelet effects and may have cardioprotective properties by replenishing high-energy phosphate stores in endothelial cells and myocytes; inhibiting cytokine release from mononuclear cells, oxygen free radical formation, and neutrophil activity and accumulation; reducing cardiomyocyte apoptosis; improving microvascular function; and invoking preconditioning responses. After favorable results were seen in preclinical investigations and several pilot trials, 236 STEMI patients within 6 hours of symptom onset treated with fibrinolysis were randomized to a 3-hour 70-μg·kg⁻¹·min⁻¹ adenosine infusion versus placebo in the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial. In 92 patients with anterior infarct size assessed by technetium-99m sestamibi single-photon-emission computed tomography imaging on day 6, the primary end point of the study, was significantly smaller in patients treated with adenosine compared with placebo (median, 11% versus 27%; P=0.02), an effect similar to that observed in AMISTAD-1. In the Attenuation by Adenosine of Cardiac Complications (ATTACC) trial of 608 patients randomized to a 6-hour infusion of low-dose adenosine (10 μg·kg⁻¹·min⁻¹) or placebo after fibrinolysis, left ventricular systolic function assessed by echocardiography at 4 days was not improved, although a trend toward reduced mortality was observed in patients with anterior infarction receiving adenosine. Considered collectively, these studies support a possible beneficial impact of adenosine in patients with anterior infarction undergoing reperfusion therapy, although further studies are required to confirm whether adenosine or adenosine analogs truly reduce infarct size and improve clinical outcomes.

**Novel Device-Based Approaches**

Several novel catheter-based systems have been investigated to enhance myocardial salvage. The recognition that distal thromboembolization is ubiquitous during primary PCI and frequently results in diminished microcirculatory perfusion or gross macroscopic emboli, both of which have been associated with increased infarct size and reduced survival, has led to the performance of 21 trials in which 3721 patients undergoing primary PCI have been randomized to standard therapy or to pretreatment with distal protection devices, passive thrombus aspiration catheters, or active thrombectomy systems, as summarized in a recent meta-analysis. These devices retrieve thrombus and/or atheroma in most of the patients treated; in many of the trials, they have reduced distal embolization and resulted in enhanced TIMI grade 3 flow, enhanced contrast opacification of the microcirculation (myocardial blush), and more complete ST-segment resolution. In this meta-analysis, however, survival was not found to be improved by the routine use of either distal protection or thrombectomy devices (Figure 5), nor has infarct size been shown to be reduced. Whereas the results with distal protection devices have been neutral (no benefit but no harm), in the largest randomized trial using an active thrombectomy catheter (n=480), randomization to rheolytic thrombectomy paradoxically resulted in lower rates of TIMI grade 3 flow (91.8% versus 97.0%; P<0.02), increased infarct size (mean, 12.5% versus 9.8%; P=0.03), and greater 30-day mortality (4.6% versus 0.8%; P=0.02). Similarly, in the largest randomized trial evaluating a thrombus aspiration catheter in which myocardial recovery was assessed, the final median infarct size was 15% in patients assigned to thrombus aspiration followed by PCI versus 7.5% after primary PCI alone (P=0.004). The lack of infarct size reduction with distal protection and thrombectomy devices was unexpected but may reflect the fact that infarct size often is complete after 2 to 3 hours of coronary occlusion and thus...
the angiographic benefits have not translated into reduced mortality. Moreover, use of these devices may entail a 15- to 20-minute delay to reperfusion and in some cases causes embolization or other complications that otherwise offset any potential benefits.

More recently, the results of the single-center Thrombus Aspiration Compared to Balloon Angioplasty (TAPAS) trial have been reported in which 1071 patients with STEMI with symptom onset within 12 hours were randomized before angiography to a simple aspiration catheter before PCI or to primary PCI alone.\(^{105}\) Adjunctive aspiration resulted in enhanced rates of normal angiographic myocardial perfusion (blush) and ST-segment resolution. At 30 days, mortality tended to be less in patients treated with thrombus aspiration (2.1% versus 4.0%; \(P=0.07\)), a trend that became significant at 1 year (\(P=0.04\)).\(^{106}\) The reduction in mortality was greater, however, than would have been expected by the modest gains in angiographic and ECG reperfusion achieved with aspiration, and surprisingly, the results with aspiration were not relatively better in patients with thrombus or occluded coronary arteries. Direct stenting without predilatation also was more frequent after thrombus aspiration, which may have contributed to the favorable results.\(^{107}\) Infarct size was not measured in this study. Thus, these results require confirmation in a multicenter randomized trial (with infarct size determination) before they can be considered definitive. Nonetheless, in contrast to the use of distal protection devices or active thrombectomy systems, simple passive aspiration may be performed quickly and with few complications and thus may be recommended in patients with large angiographic thrombus.

Supersaturated oxygen delivery and systemic hypothermia have shown potential to improve left ventricular function because of either late or ineffective reperfusion therapy, stem cell therapy, or the presence of microvascular obstruction.\(^{108}\)}

**Figure 5.** Pooled analysis of the 30-day mortality from 18 randomized trials in which 3472 patients with STEMI undergoing primary PCI were randomized to treatment either with or without distal protection devices (6 trials, 1331 patients) or thrombectomy systems (12 trials, 2141 patients) to protect the distal microcirculation. Data from Reference 101. Note that the data vary slightly from Reference 101 because of presentation of relative risks (RRs) rather than ORs.

<table>
<thead>
<tr>
<th>Microcirculatory protection device</th>
<th>Control</th>
<th>RR [95% CI]</th>
<th>RR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal protection devices</td>
<td>24/659</td>
<td>0.65 [0.35, 1.21]</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Thrombectomy devices</td>
<td>21/1065</td>
<td>1.32 [0.76, 2.29]</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>All</td>
<td>45/1724</td>
<td>0.96 [0.64, 1.45]</td>
<td></td>
<td>0.86</td>
</tr>
</tbody>
</table>

**Figure 6.** Results from the AMIHOT trial in which patients with STEMI were randomized to intracoronary supersaturated oxygen vs control after successful PCI within 24 hours. Infarct size was measured at 14 days by technetium-99m sestamibi imaging, with the results stratified according to infarct location and time from symptom onset to reperfusion.
cell therapy represents a promising investigational therapeutic alternative to promote myocardial recovery. After promising experimental and uncontrolled or open-label clinical studies with intravascular and intramyocardial administration of blood- or bone marrow–derived progenitor cells, the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial was performed in which 204 patients were randomized to intracoronary injection of bone marrow mononuclear cells (consisting of a heterogeneous mix of hematopoietic, mesenchymal, and other progenitor cells) versus placebo 3 to 7 days after successful primary PCI in STEMI. The primary end point, an improvement in left ventricular ejection fraction from baseline to 4 months assessed by paired contrast left ventriculography, was significantly greater in the treatment group than in the placebo group (mean increase, 5.5% versus 3.0%; \( P = 0.01 \)) as a result of reduced end-diastolic volumes with no change in end-diastolic volumes. Although the trial was underpowered for clinical outcomes, at the 1-year follow-up, patients receiving bone marrow mononuclear cells compared with placebo had reduced rates of composite death, reinfarction, or coronary revascularization (24% versus 41%; \( P = 0.009 \)) owing to less reinfarction (0% versus 5.8%; \( P = 0.02 \)) and revascularization (22% versus 36%; \( P = 0.03 \)) with a trend toward lower mortality (2.0% versus 5.8%; \( P = 0.28 \)).

The potential cellular mechanisms underlying the improvement in myocardial recovery and clinical events seen in this trial are undetermined but may relate to enhanced angiogenesis, autocrine and paracrine effects resulting in decreased cardiomyocyte apoptosis, myocardial fibrosis and improved microcirculatory perfusion, and/or immune modulation. There is also the prospect that infused bone marrow–derived progenitor cells may transdifferentiate into cardiomyocytes, although the likelihood of a large-scale regenerative process has been challenged.

Despite these favorable outcomes, other randomized controlled trials of bone marrow mononuclear cells in STEMI have reported negative or mixed results. It has been hypothesized that subtle differences in cell processing and storage resulting in differences in the number and functionality of infused progenitor cells may explain the discordance between trials. Regardless, a large-scale, placebo-controlled randomized trial adequately powered for clinical events is required to confirm the improvement in left ventricular function and cardiovascular outcomes noted in REPAIR-AMI. Ongoing studies also are investigating the potential of other cell types and delivery approaches in patients with recent STEMI, including peripheral blood-derived endothelial progenitor cells, immunoselected bone marrow–derived cells, autologous or donor (allogeneic) bone marrow–derived mesenchymal cells, adipose-derived progenitor cells, embryonic stem cells, and stem cell mobilization by granulocyte colony-stimulating factor or other cytokines.

**Conclusions: Intervventional Strategies in STEMI**

Over the last 3 decades, tremendous progress has been made in decreasing the case fatality rate of patients with STEMI that is attributable to the widespread use of coronary care units and effective reperfusion therapy. For patients presenting within 12 hours of STEMI onset, fibrinolytic therapy compared with placebo saves ≈2 lives per 100 treated, and primary PCI may double this benefit. However, up to one third of eligible patients with STEMI, most often women, the elderly, and those presenting without chest pain, still receive no acute reperfusion therapy. Misdiagnosis of the ECG in the emergency department also contributes to ideal candidates not receiving reperfusion therapy. Goals and training programs must therefore be established and quality control measures instituted to ensure that emergent reperfusion therapy is performed in all STEMI patients without contraindications.

Widespread consensus exists that when delivered in a timely fashion at experienced centers, primary PCI compared with fibrinolysis will save lives; enhance myocardial recovery; prevent intracranial bleeding, stroke, reinfarction, and recurrent ischemia; and otherwise enhance cardiovascular outcomes. Among patients receiving fibrinolytic therapy, strong evidence has emerged that optimal outcomes are achieved by routine immediate or early catheterization and PCI thereafter. Urgent diagnostic cardiac catheterization with subsequent intervention as appropriate also is recommended for patients presenting with non-STEMI, those with a nondiagnostic ECG, or patients presenting 12 to 48 hours after symptom onset. This increasing emphasis on routine PCI in patients with acute coronary syndromes regardless of whether fibrinolytic therapy is administered can best be met by establishing “interventional centers of excellence” with ambulance diagnosis of AMI and subsequent selective routing, similar to the trauma center model, which will further reduce mortality by requiring optimized critical pathways to reduce door-to-balloon times, greater operator and institutional volumes, and careful quality control with internal and external feedback. Although such societal policy changes, requiring the adoption by many stakeholders with varying interests, will no doubt not come easily, the benefits to the population are likely to be profound. Finally, ongoing investigation into acute reperfusion therapy, coupled with appropriate use of implantable defibrillators and secondary prevention through optimal medical therapy and risk factor reduction, promises to further improve outcomes for patients with STEMI.

**Disclosures**

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**References**


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