Current Status and Future Prospects for Acute Myocardial Infarction Therapy

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Abstract—Considerable new evidence has accumulated in randomized trials of myocardial reperfusion. The trials of catheter-based reperfusion compared with fibrinolytics have shown an advantage for angioplasty and stenting over pharmacologic therapy, even accounting for delays in transporting patients from facilities with intervention capabilities. On the basis of the recent trials, it is recommended that a regional center for infarct intervention be set up akin to regional trauma centers in the United States. Now that we have entered the third decade of myocardial reperfusion therapy, we can expect iterative improvement in all aspects, and ultimately a fused approach of pharmacology and mechanical therapies—to achieve the optimal outcomes and continue to lower the toll of fatality and morbidity of acute myocardial infarction (MI). (Circulation. 2003;108[suppl III]:III-6-III-13.)

Key Words: fibrinolysis ■ myocardial infarction ■ thrombosis

Since the mid-1980s, there has been steady refinement in our approach to acute ST-elevation myocardial infarction (STEMI). Although intravenous streptokinase was the initial pharmacologic reperfusion therapy validated to improve survival,1 more recent trials have shown the superiority of tissue plasminogen activator (t-PA), and the equivalence of t-PA with reteplase or tenecteplase.2–4 Furthermore, catheter-based reperfusion has been assessed in many comparative trials, and has been shown to be superior to fibrinolitics for reduction of the composite of death, reinfarction, or stroke.5–7 The role of antiplatelet adjunctive therapy has also been studied extensively, with demonstration of the importance of aspirin in pharmacologic reperfusion and the use of platelet glycoprotein (GP) IIb/IIIa blockade with catheter-based reperfusion.8–11 Catheter-based reperfusion has been increasingly applied in preference to pharmacologic therapy in hospitals throughout the United States, Europe, and Australasia. Yet the practical aspects of providing continuous, 24/7 coverage for this strategy, involving hospitals without facilities for percutaneous coronary intervention (PCI), has only recently received attention. Accordingly, there are many important residual and yet unsettled questions such as whether to transport patients on an emergency basis to a site where PCI can be performed as compared with administering fibrinolytic therapy. In the 3 trials, Danish Multicenter Randomized Trial on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI)-2 (DANAMI-2 data were presented at the 51st Annual Scientific Sessions of the American College of Cardiology, Atlanta, GA, March 2002), Primary Angioplasty in Patients Transferred from General Community Hospitals to Specialized PTCA Units with or without Emergency Thrombolysis (PRAGUE)-2,12 and Air Primary Angioplasty in Myocardial Infarction (Air PAMI),13 there was remarkable concordance of benefit for catheter-based reperfusion over on-site fibrinolytic therapy for the reduction of the cluster of death, reinfarction, or stroke (Figure 1). Across the trials, it is striking to note the similarity in the major adverse event rates in the transport-PCI group, at 8–8.5%, and in the fibrinolytic assigned patients at 13.5–15%, for a consistent 40–50% reduction of the primary event cluster.

These results were not anticipated because of the intrinsic delays associated in transporting patients to specialized centers. The DANAMI-2 trial was performed in Denmark, and the 5 PCI sites had only limited experience as a regional PCI center before initiation of the trial. Similarly, the PRAGUE-2 trial was accomplished in the Czech Republic with minimal
delay times from the patient entry to the door of the community hospital to the balloon inflation in the infarct vessel at the referral hospital. Although a smaller trial, the Air PAMI results were quite comparable. The delay times of only 30 minutes for transport in the DANAMI-2 and PRAGUE-2 trials are particularly noteworthy, because this rapid patient transfer and cath laboratory readiness may be difficult to replicate in many geographic locations. These 3 trials, in aggregate, highlight the advantage of a catheter-based reperfusion approach and the overriding benefit of this strategy compared with the more practical and widely available administration of intravenous fibrinolytics. Another recent trial, the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT), also provided evidence to support this tenet, but in a different matrix of hospitals. In this relatively small randomized trial, PCI was performed in 11 community hospital centers in Maryland and Massachusetts that had no bypass surgery backup or concurrent experience in elective PCI procedures. A significant advantage of PCI over fibrinolytic therapy for the death, MI, and stroke endpoint was confirmed. One particularly intriguing explanation is the relative time-independent benefit of angioplasty compared with fibrinolytic therapy as reflected in pooled analysis by Zijlstra et al. (Figure 2). Patients typically present with significant delays to the hospital, in the order of 2.5–3 h. PCI would be expected to more reliably achieve reperfusion. Alternatively, the extent of myocardial reperfusion, without a significant residual stenosis of the culprit epicardial artery lesion, may be contributing. Irrespective of the mechanism of the benefit of PCI, these results suggest the need for a revamped approach to evolving MI care in the United States.

With MI by far the most important cause of death and disability of all of the medical conditions (Figure 3), the recent data provide impetus to set up regional specialized centers of MI intervention. Such a system is operational for trauma centers throughout most of the states in the United States. Each regional trauma center provides particular expertise and quality assurance, and receives preferential transfers in order to fulfill the model of centers of clinical excellence. With trauma a much less prominent cause of death in the United States compared with acute MI, it seems particularly appropriate that a parallel entity of specialized centers for MI intervention be set up. This would allow an increasing number of patients to receive state-of-the-art care for acute MI and translate the evidence-based PCI advantage to routine clinical care.

Fibrinolytic Therapy Is Validated and an Important Alternative Reperfusion Strategy

Fibrinolytic therapy is the most intensively studied therapeutic intervention in the history of randomized trials with clearest survival benefit. Whereas catheter-based reperfusion has been shown to provide incremental benefit, no comparative trial has shown mortality reduction. The recent transport trials incorporated minimal use of rescue PCI after fibrinolytic therapy (2.5% in DANAMI-2 and 6.4% in PRAGUE-2), and the time of transport and cumulative was “door-to-balloon” remarkably fast. Notwithstanding these points, the aggregate data suggests that if PCI can be performed rapidly by an experienced team and site, the composite of death, reinfarction, and stroke will be favorably affected.

Facilitated and Rescue PCI

One critique of the transport trials was a very limited proportion of patients who underwent rescue PCI if there was no ECG evidence of reperfusion (<70% resolution of ST-segment elevation) at 60–90 min after fibrinolytic therapy was initiated. In the DANAMI-2 trial, for example, only 2.5%
of the patients underwent rescue PCI. A more reflective randomized trial, known as Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial infarction (CAPTIM), compared PCI versus a strategy of fibrinolytic therapy with rescue PCI in 26% of patients. The results, as shown in Figure 4, provide much less compelling evidence of the superiority of the PCI approach. There has been considerable study of ECG ST-segment resolution, with validation that this accurately represents tissue level perfusion by scintigraphic sestamibi myocardial perfusion study. Accordingly, the appropriate use of rescue PCI needs careful consideration, because it may provide a means of improving the adverse outcome profile of patients receiving intravenous fibrinolytic therapy. A major practical problem in the use of rescue PCI is that the patients have proven resistant to a full dose of fibrinolytic therapy, and emergency PCI is usually accompanied by conjunctive use of intravenous platelet GP IIb/IIIa inhibitor. This sets up a bleeding complication liability with full doses of fibrinolytic therapy, GP IIb/IIIa blockade, aspirin, and anticoagulation. With the recent validation of combination fibrinolytic therapy (at half dose) and GP IIb/IIIa blockade for equivalence in outcomes, there may be more rationale for using this strategy when rescue PCI can be performed.

Importantly, it would be ideal to develop a pharmacologic “bridging” regimen that achieved myocardial reperfusion rapidly, but without the risk of significant hemorrhage, and particularly intracranial bleeding, which characterizes intravenous fibrinolytic therapy. Furthermore, such a drug strategy would support rather than undermine the PCI success, as shown in Figure 4, provide much less compelling evidence of the superiority of the PCI approach. There has been considerable study of ECG ST-segment resolution, with validation that this accurately represents tissue level perfusion by scintigraphic sestamibi myocardial perfusion study. Accordingly, the appropriate use of rescue PCI needs careful consideration, because it may provide a means of improving the adverse outcome profile of patients receiving intravenous fibrinolytic therapy. A major practical problem in the use of rescue PCI is that the patients have proven resistant to a full dose of fibrinolytic therapy, and emergency PCI is usually accompanied by conjunctive use of intravenous platelet GP IIb/IIIa inhibitor. This sets up a bleeding complication liability with full doses of fibrinolytic therapy, GP IIb/IIIa blockade, aspirin, and anticoagulation. With the recent validation of combination fibrinolytic therapy (at half dose) and GP IIb/IIIa blockade for equivalence in outcomes, there may be more rationale for using this strategy when rescue PCI can be performed.

Regional Centers for MI
No matter the outcome of these ongoing trials, there should be readiness for specialized centers to provide timely, high-quality, catheter-based reperfusion. Such centers would have a critical role whether they are providing primary, rescue, or facilitated coronary intervention. This requires the availability, on a continuous basis, of an on-call team with particular expertise from having performed a high volume of emergency coronary intervention procedures. The high volume is not only referring to the center’s track record over the past few years, but also the experience of the senior operator. Furthermore, the hardware of the catheterization laboratory, consisting of high resolution cineangiographic equipment, along with a full inventory of guide catheters, wires, balloons, stents, and emboli protection devices, is required. Expertise in the use of pharmacologic therapy, such as intracoronary adenosine or nitroprusside, fibrinolytics, and parenteral antiplatelet and anticoagulant treatment, will be imperative. Management of the high-risk patient with hemodynamic compromise is yet another dimension of such a center. This includes not only the use of an intra-aortic balloon pump, but also the immediate triage to bypass surgery, or the use of extracorporeal membrane oxygenation or left ventricular assist devices in young patients with a devastating MI who might be eligible for transplantation. The unusual but important patient with intractable ventricular arrhythmias in this setting mandates the cooperative effort of senior electrophysiologists. Similarly, life-threatening bleeding may require emergency consultation with hematologists or gastroenterologists for optimal management. In aggregate, the require-
ments for a regional center are extensive, and the credentialing of hospitals and operator teams would be necessary to ensure quality standards, and yearly review of results would help sustain and promote the highest level of care. Outcomes that can be tracked include time-to-treatment (e.g., door-to-balloon), successful reperfusion of the infarct vessel, survival, congestive heart failure, reinfarction, transfusion requirements, and use of appropriate conjunctive medications, such as aspirin or statins. Finally, this is a very dynamic field, and the standards continue to be refined. ideally, all of the regional infarct centers would participate in clinical research projects to stay fully abreast of the latest developments in this arena rather than awaiting the slower process of trial publication and change in guidelines to affect state-of-the-art clinical practice.

Combined Fibrinolytic and Platelet GP IIb/IIIa Blockade

Two trials have assessed the clinical outcome profile with half-dose fibrinolytic therapy and GP IIb/IIIa blockade. In the largest trial of 16,600 patients, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-V, there was no difference in mortality at 30 days or 1 year for combination therapy compared with reteplase monotherapy.19,20 There was a significant reduction in reinfarction for combination therapy, but this was achieved with significant excess in bleeding complications. Importantly, for younger patients, and especially those <60 years of age, there appeared to be a protective effect for the combination with significantly less intracranial hemorrhage (ICH). On the other hand, those patients >75 years of age appeared to have excessive risk of ICH with combination therapy. Although a smaller trial of 6000 patients, ASSENT-3 had similar findings using tenecteplase as the fibrinolytic.21 Interestingly, the combination of tenecteplase and enoxaparin achieved a similar outcome profile for reduction of the death and reinfarction composite, along with less bleeding complications, compared with the results obtained with tenecteplase and abciximab.

High-risk subsets may derive particular benefit from combination therapy. Mukherjee et al. have shown recently that the patients with prior coronary artery bypass grafting (CABG) had a very substantial benefit of combination therapy in the GUSTO-V trial.22 Patients with large anterior MI also appeared to have a survival benefit that was nearly 1% absolute, or 14% relative,19 in keeping with the magnitude of benefit of t-PA over streptokinase in the GUSTO-I trial for the overall cohort. Accordingly, whereas combination therapy is not useful as a routine pharmacologic strategy, it may have particular value in younger patients with prior CABG or anterior MI, and the strategy for facilitated PCI is currently being assessed in ongoing trials. It is important to point out that the decision to select particular strategies for MI will be indexed not only to survival outcomes, but also to key secondary outcomes such as reinfarction and prevention of stroke or heart failure. The advantage of combined platelet GP IIb/IIIa blockade and half-dose fibrinolitics, on an individualized basis, can be supported by the composite of expected outcome effects. For a young patient with a large MI, one would anticipate reduction of intracerebral hemorrhage, less reinfarction, and at least a trend toward less mortality. The ability for a new therapy in acute MI to show an “across-the-board” striking mortality reduction at this point in the progressive refinement of treatment strategies appears unlikely, but the use of available clinical trial evidence to extrapolate an appropriate selection from a wider study is crucial.

Figure 5. A, study algorithm for ADVANCE-MI. B, study algorithm for FINESSE. C, study algorithm for TIGER. D, study algorithm for ExTRACT-TIMI 25.
array of therapeutic choices for greater net benefit of a particular patient is attractive.

**More Potent Anticoagulation**

UFH has been the dominant anticoagulant used since the initiation of reperfusion therapy in the 1980s. An indirect anticoagulant requiring antithrombin-III as a cofactor, and readily inactivated by platelet factor-4 and plasma proteins, the biological attributes of heparin can be seen as suboptimal. This has led, in recent years, to the challenge of the use of heparin using low-molecular-weight heparins or direct thrombin inhibitors. The most favorable data comes from ASSENT-3 in which enoxaparin with tenecteplase was superior to UFH with tenecteplase for the composite of death, MI, or recurrent ischemia. This issue is being intensively studied in the ongoing Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction study 25 (ExTRACT-TIMI 25) trial in which >20,000 patients are being enrolled with randomization of enoxaparin or UFH with any fibrinolytic (t-PA, reteplase, tenecteplase, or streptokinase) selected by the physician-investigator (Figure 5). This trial of enoxaparin comes after not only ASSENT-3 but also the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and TIMI 11B trials, both of which validated the benefit of enoxaparin over heparin in patients with acute coronary syndromes (unstable angina and non-ST-elevation MI). In addition to these completed trials in patients with acute coronary syndromes, there is a large ongoing trial known as Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein GP IIb/IIIa Inhibitors (SYNERGY) that is currently testing enoxaparin or heparin in acute coronary syndromes, and the ADVANCE-MI trial, a facilitated PCI project, as depicted in Figure 5. The recently completed ASSENT-3 PLUS trial, in which tenecteplase plus enoxaparin or tenecteplase plus UFH was administered in the ambulance, confirmed the finding that elderly patients (age >75) need to have their enoxaparin and fibrinolytic dose adjusted down. In this trial of 1,639 patients, the ICH rate was 2.2% in the combined tenecteplase plus enoxaparin group compared with 0.97% in the tenecteplase plus UFH group (P=0.047). However, almost all of the ICH events occurred in the age >75 years group, and there was a significant interaction between patient age and the risk of bleeding. This was taken into account in the ExTRACT-TIMI 25, ADVANCE-MI, and SYNERGY large-scale programs, which lowered the dose of enoxaparin in patients ≥75 years of age.

There have also been studies using direct thrombin inhibitors, beginning with the GUSTO II trial that tested hirudin, and most recently, the large Hirulog Early Reperfusion/Occlusion (HERO)-2 trial that compared bivalirudin and UFH, both with streptokinase as the fibrinolytic agent. In both GUSTO II and HERO-2 there was modest evidence of reduced reinfarction but no decrease in mortality.25,26 To date, considering the totality of data available, there is a lack of convincing evidence from the direct thrombin inhibitor trials of an advantage compared with UFH, but ongoing trials will address this more definitively.

**New Devices**

There is considerable interest in extrapolating recent advances in new devices from other settings in interventional cardiology to acute MI. It is clear that most patients do not achieve TIMI 3 reflow after emergency PCI, and that the most likely explanation for incomplete tissue level perfusion is embolization of thrombus, with or without microparticulate atheromatous debris. Recently, the study by Henriques et al. documented a compromised long-term survival in patients who had suffered apparent angiographic embolization with their PCI for acute MI (Figure 6). The Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial, conducted in patients with saphenous vein graft lesions with an emboli protection device known as the PercuSurge, served as a key proof-of-concept. In that trial, reduction of peri-procedural MI was substantial among patients who were assigned emboli protection.29 It is likely that a similar extent of reinfarction or infarct expansion can be avoided in the setting of acute MI, and ongoing trials such as Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris (EMERALD) are evaluating the use of emboli protection with emergency coronary intervention. In order for successful percutaneous intervention to be accomplished in the infarct vessel, it is likely that embolization of clot, with or without atheromatous debris, is obligatory. As the emboli protection devices are better engineered and become less costly, it is quite likely that such devices will ultimately be considered standard of care and be used in virtually all patients undergoing acute MI intervention. But this will take at least a few years, given the incubation period for not only better designs, but also validation in clinical trials.

In a parallel course of development that has received considerable attention, the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Native Coronary
TABLE 1. Regeneration of Myocardium: Success Across Multiple Species, Labs, Routes

<table>
<thead>
<tr>
<th>Species</th>
<th>Cell Source</th>
<th>Time</th>
<th>Route</th>
<th>LV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlic32</td>
<td>Mice</td>
<td>3–5 h</td>
<td>IM</td>
<td>↑</td>
</tr>
<tr>
<td>Kocher33</td>
<td>Rats</td>
<td>2 days</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Jackson36</td>
<td>Mice</td>
<td>4 wks</td>
<td>BMT</td>
<td>↑</td>
</tr>
<tr>
<td>Fuchs35</td>
<td>Pigs</td>
<td></td>
<td>Bone marrow</td>
<td></td>
</tr>
<tr>
<td>Orlic36</td>
<td>Mice</td>
<td>4 wks</td>
<td>IV</td>
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* LV, left ventricular; IM, intramuscular; G-CSF, granulocyte-colony stimulating factor; BMT, bone marrow transfer; IV, intravenous.

Artery Lesions (RAVEL)30 and SirolImUS-eluting stent in de novo Native Coronary Lesions (SIRIUS) trials (SIRIUS data were presented at the 52nd Annual Scientific Sessions of the American College of Cardiology, Chicago, IL, March 2003), have demonstrated that stents coated with a rapamycin derivative, sirolimus, have a markedly lower rate of in-stent restenosis during extended follow-up. Although coated stents have not yet been specifically tested in the acute MI setting, it is likely that they will be used when commercially available given the extensive reduction in restenosis. There is an overall sense that the infarct vessel carries a higher rate of renarrowing during follow-up (compared with the coronary arteries not involved in acute MI), and that the sirolimus and other coated stents do not pose a thrombotic jeopardy of subacute stent thrombosis. However, it will be helpful and important to document these issues in the setting of acute MI.

Hypothermia to 32–34°C has been shown to ameliorate outcomes in patients who suffer cardiac arrest in a randomized trial.31 Now that there are devices that can be rapidly inserted into the central veins via percutaneous technique and achieve core hypothermia, this strategy is being tested for acute MI. There are hemodynamic effects of hypothermia including increased systemic vascular resistance and diminished cardiac output, along with metabolic effects such as hyperglycemia. We will need to have data from rigorously performed randomized trials before it is possible to suggest that hypothermia is an attractive option for patients with acute MI.

Myocardial Regeneration

Perhaps the most innovative and exciting approach to acute MI lies with the potential to purposefully induce new myocyte formation. The concept has received considerable attention in the past couple of years, with several critical observations. First, in a variety of species, it has been shown that myocardium can be regenerated from hematopoietic or mesenchymal (stromal) stem cells derived from the bone marrow. In some of these experimental models, not only are myocytes generated but there is improved functionality of the myocardium in the region or even amelioration of global ventricular function (Table 1).32–36 Second, the phenomena of homing of stem cells to injured myocardium has been intensively studied, and particular factors have been implicated in orchestrating the process that routes stem cells to the tissue in need.37 Third, a variety of cells can be transformed to myocytes including embryonic stem cells, hematopoietic cells from the bone marrow, mesenchymal or stromal cells from the marrow, or endothelial progenitor cells.38 Fourth, in patients who sustain acute MI there is a natural response of recruiting new myocytes in the weeks that follow the infarct.39 And fifth, early studies in humans with direct intracoronary infusion or injection of bone marrow-derived cells have been shown to be feasible and associated with improved ventricular function.40,41

This series of seminal studies sets the foundation for clinical trials of stem cells for acute MI. The optimal methods for mobilization of stem cells, the precise biologic profile of particular cell lines, refinements and amplification of homing and successful transdifferentiation, and long-term function of these regenerated myocytes all need careful assessment. Whether or not the new myocardial cells can be developed in adequate quantity to acutely or ultimately restore cardiac function, and whether there will be electrical instability as a result, or oncologic potential of the cells at a future point, all stand as looming questions.42 But the excitement of this potential has captured the attention of all of the active cardiovascular investigators. The complementarity of myocardial reperfusion and myocardial regeneration seems attractive, particularly because we have been unable to find ways to get patients to present early enough for maximal myocardial salvage, and our pharmacologic approaches have not yielded a major, incremental advance in success over the past decade. But considerably more headway will be required to know whether this conceptual breakthrough will become a clinical reality at some point.

Conclusion

Although MI is the most important cause of death and disability in Western society, there has been steady refinement in our therapeutic approaches. In recent years, catheter-based reperfusion has been shown to be clearly superior to pharmacologic therapy, and consideration for regional centers of excellence is clearly imperative to translate the new body of evidence into clinical practice. It is clear that such specialized centers will require continuous quality assurance, such as constant readiness on a 24/7 basis, which has, until this point, not characterized most sites for emergency coronary intervention.43 The “facilitative” pharmacologic approach is being extensively assessed in ongoing trials, and, at the same time, there are trials to assess improved adjunctive therapy, such as low-molecular-weight heparin instead of unfractionated heparin. We clearly can do better with appropriate triage of reperfusion therapy, since recent registry data indicate that 30% of patients who would otherwise qualify are not getting the therapy.44 Moreover, systems can be re-evaluated to smooth out the timing of therapy, as a recent British report that empowered nurses to administer fibrinolytic therapy showed a marked reduction in the door-to-treatment time without mistaken diagnosis.45 In the context of improving the catheter-based approach, the potential for routine emboli protection as a means of achieving more complete, tissue-level reperfusion is attractive and currently being explored. While the field of myocardial regeneration is in a nascent phase, it clearly has enormous potential to help us deal with the patient who has suffered quite extensive myonecrosis. Now that we have entered the third decade of myocardial reperfusion therapy, we can expect iterative...
improvement in all aspects, and ultimately a fused approach of pharmacology and mechanical therapies, to achieve the optimal outcomes and continue to lower the toll of fatality and morbidity of acute MI.

References


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