Fibrinolysis for Acute Myocardial Infarction

The Future Is Here and Now

Paul W. Armstrong, MD; Désiré Collen, MD, PhD; Elliott Antman, MD

"The reports of my death are greatly exaggerated."
—Mark Twain, 1897, cable from London to the Associated Press

Pharmacological reperfusion therapy for acute myocardial infarction was incorporated into the armamentarium of clinicians over 15 years ago and has had an extraordinarily beneficial impact on outcome of patients with ST-elevation myocardial infarction (STEMI). There are 3 fundamental components to pharmacological reperfusion; these consist of the core fibrinolytic agent as well as the accompanying antithrombotic and antiplatelet conjunctive therapies. No contemporary therapy in cardiovascular medicine has been as carefully and critically examined in multiple large randomized trials. These have comprehensively examined the efficacy, safety, and impact of novel therapeutic third-generation fibrinolytics and advances in conjunctive therapies aimed at enhancing restoration of myocardial flow in the epicardial infarct-related coronary artery.1–3

Evolution of Pharmacological Reperfusion Regimens

The tissue plasminogen activator (tPA) congeners tenecteplase (TNK-tPA) and reteplase (rPA) that possess initial plasma half-lives of 15 to 30 minutes constitute the newest, most conveniently administered bolus fibrinolytics. They not only reduce the potential for medication errors but also greatly simplify the prospects of prehospital fibrinolysis.2–4 Although these newer agents do not confer additional mortality reduction over that achieved by the 90-minute weight-adjusted accelerated t-PA regimen, the enhanced fibrin specificity of TNK-tPA results in a significant reduction in systemic bleeding.4 Whereas conjunctive therapy with intravenous glycoprotein IIb/IIIa (IV GP IIb/IIIa) inhibitors enhances epicardial flow and myocardial perfusion and reduces reinfarction, these advantages have not resulted in the expected improvement in survival.5,6 Indeed, the increase in systemic bleeding and apparent excess of intracranial hemorrhage among STEMI patients over 75 years has led to reassessment of the suitability of combination reperfusion with IV GP IIb/IIIa inhibitors and reduced dose fibrinolysis.7,8 Currently, the combination of full dose fibrinolysis and low molecular weight heparin or a direct antithrombin appears to be an attractive strategy because of reduced reinfarction and recurrent ischemia.8,9

The major goal of reperfusion therapy is to minimize the time during which the culprit coronary artery remains occluded by rapidly achieving high quality reperfusion at both the epicardial and microcirculatory level and preventing reocclusion after initially successful fibrinolysis. Although Thrombolysis In Myocardial Infarction (TIMI 3) coronary flow has traditionally been viewed as the most reliable surrogate of successful coronary reperfusion, it is now clear that this is an inadequate measure of myocardial perfusion in many patients (irrespective of how it is achieved).10,11 The most readily available and clinically useful tool for assessing reperfusion success is the extent of ST-segment resolution from the baseline electrocardiogram; hence, >50% or 70% ST resolution within the first 60 to 180 minutes after therapy

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Evolution of Timing of Initiation of Pharmacologic Reperfusion

![Diagram](Image)

Figure 1. The evolution of timing and location for administration of fibrinolytic therapy. Initially reserved for intracoronary administration in the cardiac catheterization laboratory, it then devolved progressively to the coronary care unit (CCU), emergency department (ED), and ultimately to the prehospital arena either in the ambulance or home. As definitive therapy moves closer to the time of symptom onset, there is greater preservation of ischemic myocardium and enhanced clinical outcome.

provides excellent insight into the ultimate infarct size, left ventricular function, and survival.12,13

Major evolution in both the location and timing of fibrinolysis has occurred since the initial intracoronary administration of streptokinase in the cardiac catheterization laboratory over a quarter century ago14 (Figure 1). Moving the location of fibrinolysis earlier to the prehospital setting results in a significant reduction in mortality over that achieved by in-hospital fibrinolytic therapy, as demonstrated by a meta-analysis of 6434 patients (odds ratio 0.83, 95% confidence interval 0.70 to 0.98).15 Recognition of the fundamental importance of time on the impact of fibrinolytic treatment on survival was underscored by the “golden hour” metaphor, the time during which 65 lives per 1000 patients treated were saved as compared with only 10 lives per 1000 patients treated between 6 and 12 hours after symptom onset.16 Interest in moving diagnosis and therapy earlier into the field has received additional impetus on the basis of the disappointing outcome of the Rapid Early Action for Coronary Treatment (REACT) study. Despite an intense public education campaign over 18 months, the time from symptom onset to hospital presentation remained unaltered in patients with ischemic symptoms.17 Hence, a substantial further reduction in time to treatment is likely best achieved by enhancingprehospital diagnosis and therapy rather than by expecting patients to seek medical attention earlier.18

Choice of Reperfusion Strategy

The debate concerning the preferred reperfusion strategy was substantially intensified over the past year after the presentation of the much heralded but still unpublished (at the time of this writing) DANish trial in Acute Myocardial Infarction (DANAMI 2) study. In this trial, 1572 STEMI patients were randomized within 12 hours of symptom onset to a fibrinolytic versus a primary percutaneous coronary intervention (PCI) strategy in both community (n=1129) and primary PCI (n=443) hospitals.19 This study integrated an inter-institutional transfer policy for those randomized to primary PCI if it could be achieved within 3 hours. The Data and Safety Monitoring Board prematurely terminated DANAMI 2 because of the perception of “clear benefit” of primary PCI. Although DANAMI 2 did show a substantial reduction in the composite 30-day endpoint of death, re-MI, and disabling stroke (13.7% versus 8.0%; P=0.003) in favor of the primary PCI strategy, this outcome was overwhelmingly influenced by the reduction in reinfarction (from 6.3% to 1.6%; P<0.0001). Importantly, this reduction in reinfarction occurred in a clinical environment where transfer from a community hospital was considered “investigational” if a mechanical intervention after fibrinolysis was needed. Hence, urgent PCI occurred in only 2.5% of patients, even though 28% of the patients were randomized in interventional institutions. An additional study, interpreted by some as impetus to move to an overall primary PCI strategy, was conducted by the Cardiovascular Patients Outcomes Research Team (CPORT) investigators who randomized 451 STEMI patients within 12 hours of symptom onset to primary PCI versus tPA.20 Although there was no difference in mortality, there was a substantial reduction in the composite endpoints of death, re-MI, and stroke with primary PCI (17.7% versus 10.7% with tPA; P=0.03); this was again largely accounted for by a reduction in an unusually high reinfarction rate amongst fibrinolytic-treated versus PCI-treated patients (8.8% versus 4%; P=0.04). Hence, in both the aforementioned studies, which used unfractionated heparin as the antithrombin fibrinolytic partner, the recurrent infarction rate was by far the most important element in the composite endpoint and seemed unusually high relative to other trials. This is well demonstrated in Figure 2, where we compare the incidence of recurrent infarction in a number of recent STEMI studies that evaluated fibrinolysis and antithrombin therapy; it is useful to evaluate them in the context of the frequency with which mechanical cointervention with PCI was used.

Although a recent quantitative review of 23 randomized trials suggests that primary PCI is more effective than fibrinolysis in STEMI, the largest component of this difference was reinfarction.21 This work failed to provide individual patient data, thereby potentially masking heterogeneity and important treatment differences. Although the authors propose that emergency hospital transfer is both feasible and safe, a 1.2% complication rate amongst transported patients was recently reported in the Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis 2 (PRAGUE 2) study, in which 2 patients died and 3 developed ventricular fibrillation.22 In our view, this analysis is
Re-MI Post Fibrinolysis

![Graph showing Re-MI rates in recent fibrinolytic trials](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Re-MI Rate</th>
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<tr>
<td>Entire</td>
<td>4.4%</td>
</tr>
<tr>
<td>AsSENT 3</td>
<td>4.4%</td>
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<tr>
<td>HERO 2</td>
<td>6.3%</td>
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<tr>
<td>GUSTO V</td>
<td>3.7%</td>
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<tr>
<td>CAPTIM</td>
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<tr>
<td>PCI</td>
<td>14.6%</td>
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<tr>
<td>ASSENT 3</td>
<td>2.7%</td>
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<tr>
<td>DANAMI-2 DANish</td>
<td>2.7%</td>
</tr>
<tr>
<td>C-PORT</td>
<td>6.3%</td>
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Figure 2. Recurrent MI rates in recent fibrinolytic trials which utilized a conjunctive antithrombin strategy. The sample size frequency of cointervention with urgent and non-urgent PCI and the type of antithrombin therapy used are shown, and the trials with their sample sizes are presented in ascending order of their re-MI rates. ASSENT 3 indicates Assessments of the Safety and Efficacy of a New Thrombolytic regimen; CAPTIM, Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial Infarction; C-PORT, Cardiovascular Patients Outcomes Research Team; DANAMI-2, DANish trial in Acute Myocardial Infarction; ENTIRE, Enoxaparin as adjunctive antithrombin Therapy for ST-elevation myocardial Infarction RESults; GUSTO V, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HERO-2, Hiralog Early Reperfusion/Occlusion 2; TNK + Enox, Tenecteplase plus enoxaparin; PPA + Hep, reteplase plus heparin; IPA + Hep, tissue plasminogen activator plus heparin; and SK + Bival, streptokinase plus bivalirudin.

hypothesis-generating and a signal for caution rather than convincing evidence for practice change.

The Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial Infarction (CAPTIM) investigators contributed important observations by comparing prehospital fibrinolysis with primary PCI. Although these investigators reported a trend toward improvement in the composite of death, reinfarction, and disabling stroke for PCI versus fibrinolysis (6.2% versus 8.2%; P = 0.29), the 30-day mortality was 3.8% for patients receiving accelerated rtPA with unfractionated heparin versus 4.8% in those undergoing primary PCI. Hence, the major advantage was again related predominantly to a reduction in reinfarction in patients undergoing PCI. A substudy from the Plasminogen Angioplasty Compatibility Trial (PACT) investigators underscores the deleterious effects of delay in PCI-associated reperfusion. When delay to reperfusion increased from 30 through 120 minutes, there was progressively worse left ventricular function, leading these investigators to suggest that incorporation of pharmacological reperfusion may be indicated when door-to-balloon times exceeds 60 minutes. In our view, there is substantial need for caution before accepting the suggestion that widespread application of primary PCI for STEMI be undertaken, given current knowledge and available resources.

Indeed, the suggestion that a 3-hour delay in administering life-saving fibrinolytic therapy is appropriate to deliver primary PCI is, in our judgment, both unwise and unsubstantiated by current data and the realities of clinical practice. In this regard, it is especially noteworthy that the preponderance of patients undergoing treatment with primary PCI in the C-PORT study as well as the National Registry of Myocardial Infarction (NRMI) registry did so between the hours of 0800 AM and 1600 PM. Clearly, this time window does not conform to the temporal presentation of STEMI and biases the data toward shorter door-to-balloon times than are likely achievable in routine clinical practice. A primary invasive approach is neither always feasible or successful nor without hazard: Results are dependent on patient age, time to treatment, operator experience, and institutional volume.

Rather than engaging in unnecessarily strident debate on an either/or treatment proposition, STEMI patients can be best served by embracing an integrated approach to management, as depicted in Figure 3. This approach emphasizes an assessment at the earliest point of medical contact with prompt evaluation of the elapsed time from symptom onset.Antiplatelet and antithrombin therapy should be administered as early as possible in patients identified as having STEMI. Simultaneously, 4 key questions need to be addressed: (1) What is the time from symptom onset to medical contact? (2) What is the risk of the myocardial infarction based on initial clinical and electrocardiographic assessment? (3) What are the risks of fibrinolytic therapy particularly as it relates to systemic and intracranial bleeding? (4) What is the estimated time before the affected individual could be transported to a skilled interventional facility to access primary mechanical intervention? We believe ideal targets should be delivery of fibrinolysis within 60 minutes of call for medical help and within 90 minutes for the delivery of primary PCI. In patients receiving fibrinolysis, careful surveillance over the first 1 to 3 hours is critical to ensure that successful reperfusion occurs, as indicated by relief of symptoms and/or any hemodynamic or electrical instability coupled with at least 50% resolution of the initial ST elevation. Careful subsequent observation for recurrent ischemia and ischemia brought on by noninvasive testing should lead to prompt angiography and appropriate revascularization. Progress in information technology that facilitates computer-assisted electrocardiographic diagnosis, patient risk modeling, reliable transmission to a remote facility, and triage to the most appropriate healthcare facility is likely to serve patients best. For patients in cardiogenic shock, those with contraindications to fibrinolysis, and others who have rapid, ie, <90 minute, access to expert PCI facilities, primary PCI is the preferred reperfusion strategy.

For other STEMI patients, who will likely constitute the majority, early prehospital or emergency department administration of fibrinolysis may be best. Notwithstanding concerns about excess complications in the elderly, irrespective of which reperfusion strategy is used, analysis from the
Fibrinolytic Therapy Trials’ (FTT) overview provides compelling data that the greatest absolute benefit from fibrinolysis actually occurs in patients over the age of 75, ie, 40 lives per 1000 patients treated versus 20 for those under 75 years of age treated within 12 hours (Colin Baigent, Clinical Trial Service Unit, Oxford, UK, personal communication, 2002). In sharp contrast to the fibrinolytic-treated patients in the DANAMI 2 trial, it should be anticipated that in approximately 1 of 4 fibrinolytic-treated patients would require rescue PCI if clinical and/or electrocardiographic evidence of reperfusion failure were observed. Emphasis should be placed on the need to carefully evaluate patients after fibrinolytic therapy for spontaneous or provokable ischemia followed by timely in-hospital co-intervention that will minimize reinfarction (Figure 3). Risk stratification with intense secondary prevention will optimize care. Advances in PCI suggest that routine invasive study deserves consideration and further study.

In addition to early bolus therapy, the future for fibrinolysis will likely involve conjunctive therapy with a direct antithrombin or low molecular weight heparin to minimize reinfarction. The optimal pharmacological approach is still evolving. Ongoing trials are evaluating whether a combined strategy of early pharmacological therapy with further dose modification of fibrinolytic for the elderly combined with GP IIb/IIIa inhibitors ultimately facilitates more effective percutaneous intervention. Attempts to develop single bolus fibrinolytics with higher fibrin specificity (eg, pegylated staphylokinase or amidiplase) along with anticoagulants other than low molecular weight heparin (eg, factor Xa inhibitors, heparin-derived pentasaccharide) and novel antiplatelet agents are underway, but the risk/benefit and cost-effectiveness ratios remain to be determined.

In our opinion, fibrinolytic therapy, like Mark Twain, will continue contributing in a vigorous and productive way long after the premature reports of its demise.

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