Combined Thrombolytic and Platelet Glycoprotein IIb/IIIa Inhibitor Therapy for Acute Myocardial Infarction
Will Pharmacological Therapy Ever Equal Primary Angioplasty?

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The management of acute myocardial infarction (AMI) was altered dramatically with the introduction of intracoronary thrombolytic therapy in the late 1970s by Rentrop and others. The visualization of coronary artery occlusion by angiography performed during the first few hours of AMI and the removal of some of these thrombi at the time of emergent coronary artery bypass surgery convinced the medical community that AMI was, as was thought years earlier, due to "coronary thrombosis." After the publication of a number of randomized clinical trials (RCTs) of intracoronary and intravenous lytic therapy, reperfusion of acutely occluded coronary artery beds with thrombolytic therapy became a standard treatment of AMI by the mid-1980s.

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While thrombolytic therapy was gaining early acceptance as a means to achieve reperfusion, a parallel pathway for achieving reperfusion was developing with catheter-based techniques. Reports of PTCA for the management of AMI appeared in 1983. Soon a vigorous competition developed between pharmacological and mechanical methods of reperfusion. Important differences between these 2 competing approaches were apparent. Thrombolytic therapy could be initiated rapidly once the diagnosis was made, with treatment instituted in the emergency department or even before hospitalization, and it did not require the technical skills of a proceduralist for its implementation. However, because reperfusion did not occur until 60 to 90 minutes after the onset of treatment, the occurrence of successful reperfusion (or its failure) could not be ascertained with certainty by use of clinical markers, and there was an obligatory risk of intracranial hemorrhage (ICH) of 0.5% to 1.0%, with higher rates experienced in elderly patients. With PTCA, on the other hand, there was an obligatory delay between diagnosis and initiation of the procedure, and highly skilled procedural cardiologists and technical staff were required to be available 24 hours a day. Because a minority of hospitals had facilities for the support of primary PTCA, it was often necessary to transfer patients to a tertiary facility. This latter requirement markedly limited the availability of primary angioplasty. Once the emergent procedure was begun, however, some degree of reperfusion was usually achieved within a few minutes, the reperfusion status of the coronary artery was known with certainty, and the presence of severe disease best treated with emergency bypass surgery rather than angioplasty was defined. In addition, experience soon showed that there was virtually no risk of ICH and a low risk of other serious bleeding with this primary mechanical approach.

The most important difference between thrombolytic therapy and emergent PTCA, however, has to do with the achievement of acceptable reperfusion. From the earliest days of thrombolytic trials, it was known that the best clinical outcomes were associated with prompt restoration of normal or near-normal blood flow in the infarct-related artery. By the early 1990s, achievement of TIMI 3 (normal) flow through the infarct-related artery was recognized as the goal of reperfusion therapy because of the survival benefit associated with its occurrence. And there has been little doubt that mechanical reperfusion has been associated with better success at establishing TIMI 3 reperfusion of infarct arteries than has thrombolytic therapy. The most successful thrombolytic regimen for establishing reperfusion, the front-loaded tissue plasminogen activator protocol, results in TIMI 3 reperfusion in approximately 50% of treated arteries. Primary balloon angioplasty results in TIMI 3 flow in 46% to 97% of treated arteries, with most series reporting rates in excess of 70%.

A meta-analysis of a number of small RCTs comparing PTCA with thrombolytic therapy indicated that there was a survival advantage for the mechanical reperfusion technique equal to 2 lives saved per 100 treated patients at 30 days after AMI. This result was confirmed in the large-scale, multicenter GUSTO IIb trial, in which primary PTCA was associated with a survival advantage of approximately 1 life saved per 100 treated patients at 30 days. Most recently, mechanical reperfusion techniques have been further buttressed by the use of coronary stents, which appear to provide a small additional benefit compared with balloon angioplasty alone in terms of achieving complete reperfusion of the infarct-related artery bed. Although controversy persists, the playing field for these 2 competing reperfusion therapies had definitively shifted by the mid-1990s to favor mechanical techniques if the resources and technical skills that are its prerequisites were in place.

Now, the TIMI 14 investigators have provided new data that indicate that the combination of partial doses of the thrombolytic agent alteplase and the long-acting platelet...
glycoprotein IIb/IIIa inhibitor abciximab with low-dose or very-low-dose heparin infusions can achieve rates of TIMI 3 reperfusion at 60 and 90 minutes that are similar to those achieved with primary angioplasty. In addition, their results, although based on small numbers of patients in the individual dosing groups, were associated with low rates of serious bleeding and ICH. The TIMI 14 results do not stand in isolation. Gold and colleagues, in an experimental animal model of acute thrombosis, first demonstrated that synergy existed between the combination of thrombolytic and glycoprotein IIb/IIIa inhibitor agents for the purpose of achieving reperfusion. Ohman and colleagues then reported in a dose-ranging study that the short-acting platelet glycoprotein IIb/IIIa inhibitor eptifibatide when combined with alteplase resulted in 90-minute TIMI 3 flow rates of 66% compared with a rate of 39% for alteplase alone. For many years, we have strongly believed that better thrombolytic agents would never be able to achieve high rates of TIMI 3 flow with an acceptable rate of bleeding complications. The results of these investigations have opened a new era in reperfusion therapy by showing that thrombolytic agents alone will no longer be the sole pharmacological means used to achieve and maintain reperfusion. Rather, we will explore combinations of pharmacological agents aimed at different parts of the thrombosis process to determine the best means to achieve pharmacological reperfusion.

Where do we go from here? Does this mean that in the very near future, invasive cardiologists will surrender to this improved pharmacological therapy and restrict primary angioplasty to those patients with contraindications to lytic therapy? Will this new therapy result in a marked reduction in the time from diagnosis to effective treatment of AMI, with further reductions in death, myocardial infarction size, and serious bleeding? Or do we still need additional RCTs before we abandon our enthusiasm for primary angioplasty? Unfortunately, as always seems to be the case, additional trials are needed. The rates of serious bleeding and ICH associated with combined reperfusion therapy with both low-dose and very-low-dose heparin protocols need to be determined. It must also be determined what the mortality rates are for this new combined pharmacological approach to reperfusion. Because primary angioplasty has been widely accepted by the cardiology community, data derived from registries, no matter how carefully such registries are performed, are not likely to convince the interventional cardiology establishment to abandon their current heroic approach to reperfusion. Thus, at least one and likely several RCTs demonstrating equivalence or clear superiority of combination drug therapy will be needed before a major shift in treatment will occur. In many countries around the world where intravenous thrombolytic therapy has been the norm for the management of AMI, the transition to combination pharmacological therapy will likely happen more rapidly.

And what will be the best combination of pharmacological agents for achieving reperfusion? Will abciximab be the best of the platelet glycoprotein IIb/IIIa inhibitors for these purposes, or will there be a role for shorter-acting IIb/IIIa inhibitors like epifibatide or tirofiban? The use of low-molecular-weight heparin has recently been shown to be superior to unfractionated heparin in the management of acute coronary syndromes. Will low-molecular-weight heparins be of additional benefit when combined with a thrombolytic agent and a IIb/IIIa inhibitor for the purposes of pharmacological reperfusion? In addition, it will be necessary to reconsider the role of oral antithrombotic therapy after the initial intravenous infusion phase of pharmacological reperfusion therapy. Aspirin is the current accepted treatment regimen, but the addition of agents like ticlopidine or clopidogrel may help to further diminish the problems associated with reocclusion after initially successful pharmacological reperfusion. These and other questions need to be addressed. While further studies are being planned and executed, we believe that it is time for some major centers to embrace combination pharmacological reperfusion therapy and reserve primary angioplasty for patients with contraindications to its use. Carefully collected outcome data from such experience will be very helpful in assessing this new approach to the management of AMI.

The complexity of applying this new therapy should not be underestimated. In order for this therapy to be used safely, detailed institutional protocols need to be developed that include special staff training, intense and expert monitoring of these patients during therapy, and careful analysis of their outcomes. Protocols for when and how to abandon pharmacological therapy in favor of PTCA will need to be developed. Criteria for coronary angiography after thrombolytic therapy will need to be reconsidered in light of the much higher reperfusion rates that can be anticipated with the new combination therapy.

We believe that the TIMI 14 investigators have made a major contribution to the management of AMI. They have identified a combined pharmacological therapy for reperfusion that, with and without some modification, will likely prove to be equivalent or superior to mechanical reperfusion therapy. When this equivalence has been clearly defined, angioplasty of patients with AMI can be limited to those patients for whom pharmacological therapy fails or those who have contraindications to its use.

References


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