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EDITORIAL COMMENT

Combination Therapy for Acute Myocardial Infarction*

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The primary goal of therapy for acute myocardial infarction is rapid, complete and sustained restoration of infarct-related artery (IRA) blood flow. Both fibrinolytic and mechanical restoration of anterograde coronary blood flow in patients have shown to improve left ventricular function, reduce infarct size and reduce mortality (1). The benefits of myocardial reperfusion, including prevention of infarct expansion, reduction of ventricular remodeling and improvement of electrical stability, are amplified when IRA patency can be achieved quickly after the onset of symptoms, particularly in the first 2 hours—a time window that is particularly challenging for mechanical methods of reperfusion. The Global Use of Strategies to Open Occluded Arteries trial (GUSTO-I) (2) correlated 90-min patency of the IRA with mortality reduction, and the Thrombolysis in Myocardial Infarction (TIMI-I) trial (3) showed that regardless of the fibrinolytic agent used, an occluded IRA (TIMI flow grade 0 or 1) at 90 min was associated with an 8.9% 30-day mortality rate, and normal flow (TIMI 3) with a 4% mortality rate. Those with partial perfusion (TIMI flow grade 2) had an intermediate mortality rate of 7.4%. Although intravenous fibrinolytic therapy is effective in improving outcome after a myocardial infarction and can be administered early to a greater proportion of patients than is possible with percutaneous coronary intervention, its "effectiveness profile" is disappointing to most cardiologists. There is a failure to lyse occlusive thrombi in a quarter of patients; reocclusion occurs in 10% of patients; and incomplete reperfusion is present in 30% (4,5). Also, some patients have contraindications to this treatment. This is particularly true in the elderly, in whom stroke rates are high, but the potential benefit of reperfusion is greatest. Consequently, primary angioplasty has been adopted by many cardiologists, where facilities exist, as a preferred means of reperfusion.

The advantages of percutaneous coronary intervention include immediate visual assessment of reperfusion success and identification of the entire coronary and ventricular anatomy. These assessments often obviate the need for noninvasive testing before hospital discharge and can lead to an accelerated discharge and recovery of low risk patients.

In our hospital, patients treated with primary angioplasty usually spend <24 h in the coronary care unit. Because no single comparative study has been large enough to quantitate the difference between these two modalities precisely, the relative benefits of the two strategies still remain unknown. In a meta-analysis of all the trials of balloon angioplasty versus thrombolysis, the relative benefit of primary angioplasty seemed greatest in the elderly and in those with "high risk" characteristics (6). Along with the higher IRA patency rate, one study showed that patients with an open IRA after successful thrombolysis had a lower ejection fraction and greater enzyme release as compared with those treated with primary angioplasty, possibly helping to explain this difference (7). The authors hypothesize that either the induction of a systemic lytic state generates an injurious milieu that exerts adverse effects on reperfused myocardium, or that angioplasty results in a more rapid and complete restoration of TIMI flow grade 3 rates. Primary angioplasty, however, necessitates use of the cardiac catheterization laboratory and personnel equipped and prepared for emergency procedures, trained interventional cardiologists and surgical back-up availability. Therefore, it is not a practical therapy for the majority of patients.

In this issue of *JACC*, Ross et al. (8) evaluated the hypothesis that combining the two strategies may, in fact, be the best treatment. They propose that the two modalities may actually be complementary. In combining the treatments, the logistical issues of having immediate availability of the cardiac catheterization laboratory and trained interventionalists to perform emergency angioplasty, as well as the limitation of thrombolytic therapy to achieve TIMI flow grade 3, counteract one another. In the Plasminogen activator Angioplasty Compatibility Trial (PACT), 606 patients were randomized to receive a reduced dose of a short-acting thrombolytic agent (alteplase, GmbH) or placebo, followed by immediate angiography with angioplasty if indicated. All patients were treated with aspirin and heparin. The end points included patency rates on arrival to the cardiac catheterization laboratory, technical results when angioplasty was performed, complication rates and left ventricular function by treatment assignment and time to restored patency. On an intention-to-treat basis, the authors (8) found a higher rate of patency in the group that received an early bolus of alteplase, but no difference in resulting left ventricular function, which was normal in both groups.

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A previous comparison of primary angioplasty with a full-dose, long-acting, fibrinogen-depleting thrombolytic agent (streptokinase) cautioned against combination therapies by reporting excessive rates of blood transfusion and increased no-reflow and acute occlusion after angioplasty in the thrombolytic group (9). In this much larger study, as well as in other contemporary ones, it has been clearly shown that the complication rates, success rates and bleeding rates of rescue angioplasty are equivalent to those in control studies. This important observation tells us that there is no reason to hesitate to perform angiography and interventional procedures in patients who have been recently treated with thrombolysis. The difference found in earlier studies may be the result of the thrombolytic regimen used and improvements in angiographic techniques.

The PACT trial reaffirms the time-dependent nature of the open artery hypothesis: patients who experienced successful thrombolysis and TIMI flow grade 3 before angioplasty had significantly higher ejection fractions as compared with those who did not.

Ross et al. (8) discuss several limitations of their study, including the infrequent use of stents (26%) and glycoprotein IIb/IIIa inhibitors (5%), which are infrequently used during percutaneous interventions. Another consideration was the fact that the majority of the acute infarctions were lower risk (i.e., nonanterior location and overall normal left ventricular ejection fractions).

Recent data suggest that combining fibrinolytic agents (which act on the fibrinous component of a clot) with glycoprotein IIb/IIIa inhibitors and other anticoagulant agents (which act on the platelet component of the clot) may further improve the initial results of fibrinolytic treatment (10–12). Combination therapy allows the use of lower doses of thrombolytic agents, possibly reducing the risk of intracranial hemorrhage. Platelet inhibition may also reduce the risk of early reocclusion after thrombolytic therapy. Results from trials of adjunct glycoprotein IIb/IIIa inhibitors with full-dose thrombolytic therapy or reduced thrombolytic therapy have shown improvements in the rate of TIMI flow grade 3, with patency rates approaching those reported with primary angioplasty and no increase in bleeding complications (13,14).

How do we translate the findings of this study to our clinical practice? The safety and efficacy of combined platelet receptor antagonists and fibrinolytic treatment still need to be defined in future clinical trials. Pretreatment with abciximab in the emergency department before primary angioplasty appears to have little, if any, advantage in terms of "opening arteries" earlier (10). Despite its widespread occurrence, there has been no proven benefit of routinely performing angiography in all unselected patients with acute myocardial infarction. If angiography is to be performed, it should be done either at the time of hospital admission or in patients with a reduced ejection fraction or residual ischemia. Ross et al. (8) have shown that rescue angioplasty can be performed earlier at no increased risk to patients receiving thrombolytic therapy.

For now, those centers routinely performing primary angioplasty will continue to do so. The search will continue to identify a more effective lytic regimen that results in equal initial angiographic results as compared with mechanical reperfusion. We also need to come to grips with the fact that it may not be the best care to initially manage "high risk" patients (e.g., >age 70 years, diabetes, evidence of shock and anterior location) in all hospitals. Serious complications from myocardial infarction occur most often in the first few hours—possibly all such patients should be managed by the PACT method with initial treatment in the local medical center or ambulance, and then angiography at the tertiary care center. We manage severe trauma this way; shouldn't we be doing the same for acute myocardial infarction?

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