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EDITORIAL COMMENT

Pharmacological Facilitation of Coronary Intervention in ST-Segment Elevation Myocardial Infarction

Time Is of the Essence*

Bernard J. Gersh, MB, ChB, DPhil,†
Gregg W. Stone, MD‡

Rochester, Minnesota; and New York, New York

The dawn of the reperfusion era more than 3 decades ago revolutionized the management of ST-segment elevation myocardial infarction (STEMI). Over the years, reperfusion therapy has matured, a consequence of numerous trials that have defined the optimal class of fibrinolytic drugs (fibrin-specific agents), the timing of therapy, adjunctive antithrombotic and antiplatelet medication, and the role of primary percutaneous coronary intervention (PPCI). Specifically, the introduction and globalization of PPCI has resulted in another sea change in STEMI management as randomized controlled trials have clearly demonstrated the superiority of PPCI to fibrinolysis, provided that PPCI can be delivered in a timely fashion (1). Nonetheless, important

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questions remain unanswered. First, in patients presenting relatively early (within 2 to 3 h of symptoms to a hospital without PCI capabilities), what is the acceptable duration of delay for transport for PPCI as opposed to administration of immediate fibrinolytic therapy? Second, what therapies should be administered before and during transport (e.g., an antithrombin agent such as heparin or bivalirudin with a thienopyridine or a glycoprotein IIb/IIIa inhibitor)? Specifically, should fibrinolytic therapy be given immediately before transfer followed by routine emergency angiography and PCI upon arrival at the tertiary hospital (facilitated PCI)? Third, despite considerable progress, the prompt delivery of reperfusion therapy to all eligible patients does not always occur. Finally, the discordance between the high success rate of infarct artery recanalization currently achieved by PCI and the lack of effective myocardial perfusion and recovery in many patients remains an area of investigation, with discouraging results to date (2).

The present FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) substudy (3) published in this issue of *JACC: Cardiovascular Interventions* touches on several these unanswered issues. The FINESSE study was a large randomized trial designed to evaluate the effects and clinical outcomes at 90 days of 2 strategies, namely the immediate administration of abciximab alone or in conjunction with half-dose reteplase before "routine immediate" PCI (facilitated PCI) versus primary PCI with abciximab administered for the first time in the catheterization laboratory (4). The trial was neutral with no significant reduction in the 90-day primary ischemic end point in the facilitated PCI group. The present angiographic substudy (FINESSE-ANGIO) enrolled 637 of the total 2,452 patients from 6 countries in Europe. The primary substudy end point was infarct-related artery (IRA) patency (Thrombolysis In Myocardial Infarction [TIMI] flow grade 2/3) at basal coronary angiography; secondary efficacy end points were the corrected TIMI frame count, the percentage of patients achieving TIMI flow grade 3, and myocardial blush grade 2/3 after PCI—the latter being a surrogate for myocardial perfusion and presumably microvascular dysfunction. With a median time from drug administration to first angiography of 55 min, baseline IRA patency in the combination-facilitated PCI group was higher than with abciximab alone before treatment or placebo before PPCI (76.1% vs. 43.7% vs. 32.7%, respectively), but post-PCI measures of epicardial coronary flow and myocardial perfusion were similar between the groups. Nor did this early angiographic benefit translate into any improvement in clinical outcomes. Are these results paradoxical or an expected consequence of what we know or assume about the relationship between time to reperfusion and its impact upon arterial patency, myocardial salvage, and clinical outcomes?

Figure 1 is a hypothetical construct of the relationship between time to reperfusion, the extent of myocardial salvage, and reduction in mortality (5). Modifying factors include the presence of collaterals, myocardial oxygen demand, perhaps ischemic pre-conditioning, and other unidentified variables. Clinical trials in which infarct size was measured with sestamibi imaging support the "slope of the curve" concept by illustrating a narrow window for myocardial salvage within the first 1 to 3 h following symptom onset, followed by a "flat portion of the curve" during which time-to-reperfusion is less critical (6). If facilitated PCI

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From the †Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and ‡Division of Cardiology, Columbia University, Medical Center, New York, New York. Dr. Stone is on the Scientific Advisory Board of and received honoraria from Boston Scientific and Abbott Vascular, and he is a consultant to The Medicines Co., Eli Lilly, AstraZeneca, and Bristol-Myers Squibb. Dr. Gersh has relationships with Ortho-McNeil Janssen Scientific Affairs, Amorcyte, Merck, Abbott Laboratories, GE Healthcare, St. Jude, Medispec, and Boston Scientific.

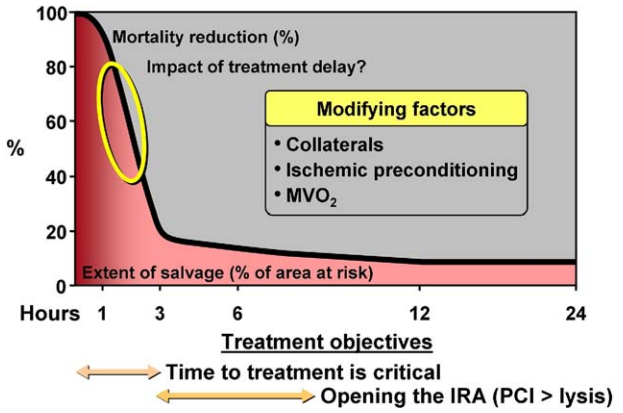

Figure 1. Relationship Between Mortality Reduction and Extent of Salvage

Postulated relationship between duration of ischemia before reperfusion, extent of myocardial salvage, mortality reduction, and goals of therapy. Reprinted, with permission, from Opie L, Gersh BJ, editors. Drugs for the Heart, 7th ed.. Philadelphia: Elsevier/W. B. Saunders, 2009. IRA = infarct-related artery; MVO_2 = myocardial oxygen consumption; PCI = percutaneous coronary intervention.

were to shorten the PCI-related delay time by achieving TIMI flow grade 3 30 to 60 min earlier, this should logically increase myocardial salvage and, depending upon the magnitude of the extent of ischemic myocardial jeopardy, could result in improved clinical outcomes. The ability to achieve incremental myocardial salvage, however, is critically dependent upon the total duration of ischemia not yet reaching the flat portion of the curve before reperfusion. Unfortunately, as previously discussed regarding the negative ASSENT 4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) trial (7), considering the approximate 2-h median delay from symptom onset to hospital arrival in the U.S and many other countries, the 30 to 60 min that lytics require for stable reperfusion, and the fact that door-to-balloon times are now routinely <90 min, reperfusion with fibrinolytic agents would be unlikely to occur much before the expected time of PCI. Moreover, this corresponds to a point on the curve in which incremental effects on myocardial salvage are unlikely. In the FINESSE-ANGIO trial, the median time from the qualifying electrocardiogram to drug administration was 41 min, and the median time from symptom onset to the start of any reperfusion therapy was 3.5 h, which already places most patients on the "flat" part of the curve, at which time earlier attainment of TIMI flow grade 3 is unlikely to provide incremental myocardial salvage compared with PPCI alone.

In contrast to FINESSE and ASSENT 4, prior series (8) have demonstrated that the presence of TIMI flow grade 3 before PPCI is associated with improved survival. In these studies, TIMI flow grade 3 occurred due to spontaneous thrombus resolution (or persistent subtotal occlusion), and indeed may reflect restoration of patency much earlier after symptom onset in contrast to the FINESSE-ANGIO study. Moreover, with facilitated PCI (as opposed to spontaneous IRA recanalization), the deleterious effects of fibrinolysis-mediated early reperfusion including platelet activation (resulting in IRA reocclusion or recurrent ischemia), and hemorrhagic complications (such as intracranial and intramyocardial hemorrhage) cannot be discounted, and may more than offset any beneficial effects of early vessel patency. This may explain why harm has been demonstrated with pharmacological facilitation in numerous trials (9).

The concept of pharmacological facilitation remains logical (if unproven), particularly in high-risk STEMI patients (e.g., anterior MI) who present early to a non-PCI center and in a setting in which transport-related delays are lengthy (10). Ideally, randomized controlled trials would be performed to determine the exact conditions under which facilitation would provide superior outcomes to PPCI alone (with only aspirin, a potent thienopyridine, and an antithrombin agent provided before transport). A remaining issue is whether a facilitated approach that mandates "routine immediate PCI" is as safe and more effective than the prevailing concept of a "pharmacoinvasive strategy," in which fibrinolytic therapy is followed by rescue PCI in unstable patients or in those with ongoing chest pain or ST-segment elevation, or by routine but delayed angiography with PCI as appropriate within 3 to 24 h in stable patients. Timing and appropriate patient selection is of the essence, however, because even the subgroup of patients in the large ASSENT 4 trial assigned to pharmacological facilitation within 2 h of symptom onset experienced no clear benefits.

Another aspect raised by the FINESSE-ANGIO study is the discordance between IRA recanalization and measures of myocardial perfusion and microvascular function. Although cardiac magnetic resonance imaging may currently be the best method for measuring the extent of left ventricular scar, microvascular dysfunction, and the potential for late myocardial recovery, myocardial blush grade and ST-segment resolution are reasonable surrogates and provide incremental predictive information (11). Studies using these indexes of myocardial perfusion highlight the fact that achieving normal epicardial coronary blood flow does not ensure normalized myocardial perfusion, microvascular function, and metabolism. Despite the demonstrated experimental efficacy of numerous cardioprotective agents and strategies in mice and other animal models, clinical trials in humans for the most part have been disappointing (2). Perhaps this relates in part to a fundamental lack of understanding of the basic mechanisms of reperfusion injury and the processes of microvascular dysfunction and irreversible necrosis (12). This may also reflect the rapid time course of these pathophysiologic phenomena; by the time the IRA

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is recanalized in the clinical setting, it is already too late to influence many of the biochemical and cellular derangements present in acute myocardial injury (13).

As PPCI has matured and become widely implemented, the emphasis has somewhat shifted away from the nature of the therapy toward enhancing the rapid delivery of care to all eligible patients. Recent data have demonstrated a gratifying decline in the time from hospital presentation to the onset of therapy. Unfortunately, however, little progress has been made in overcoming one of the major hurdles to early reperfusion—the time from symptom onset to presentation (14).

For the present, there is need for a trial of pharmacological recanalization as an adjunct to PCI in patients presenting early (<1 to 2 h) in whom substantial delay (>2 h) to PCI is anticipated, particularly in patients with large infarcts or who are hemodynamically unstable (9). Nonetheless and realistically, the benefits of this approach will be limited as long as the time-to-presentation is in the range of 90 to 120 min for the majority. For decades, we have appreciated that acute myocardial infarction is a time-critical phenomenon and that early therapy is crucial for myocardial recovery, especially in the hyperacute phase, when "time is myocardium." Educating the public to seek treatment at an early stage after symptom onset is likely to reduce mortality to a greater degree than pharmacological facilitation before PCI, although translation of this goal to reality in a community setting is and will continue to be extremely difficult.

Reprint requests and correspondence: Dr. Bernard J. Gersh, Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55905. E-mail: gersh.bernard@mayo.edu.

REFERENCES

1. Gersh BJ, Antman EM. Selection of the optimal reperfusion strategy for STEMI: does time matter? Eur Heart J 2006;27:761–3.
2. Prasad A, Stone GW, Holmes DR, Gersh B. Reperfusion injury, microvascular dysfunction, and cardioprotection: the "dark side" of reperfusion. Circulation 2009;120:2105–12.
3. Prati F, Petronio S, Van Boven AJ, et al., for the FINESSE Angiographic Substudy Investigators. Evaluation of infarct-related coronary artery patency and microcirculatory function after facilitated percutaneous primary coronary angioplasty: the FINESSE-ANGIO (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events–Angiographic) Study. J Am Coll Cardiol Intv 2010;3:1284–91.
4. Ellis SG, Tendera M, de Belder MA, et al., for the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205–17.
5. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA 2005;293:979–86.
6. Stone GW, Dixon SR, Grines CL, et al. Predictors of infarct size after primary coronary angioplasty in acute myocardial infarction from pooled analysis from four contemporary trials. Am J Cardiol 2007;100:1370–5.
7. Stone GW, Gersh BJ. Facilitated angioplasty: paradise lost. Lancet 2006;367:543–6.
8. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. Circulation 2001;104:636–41.
9. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet 2006;367:579–88.
10. Henry TD, Larson DM. The ideal reperfusion strategy for the ST-segment elevation myocardial infarction patient with expected delay to percutaneous coronary intervention: paradise lost or paradise renamed? J Am Coll Cardiol Intv 2009;2:931–3.
11. Sorajja P, Gersh BJ, Costantini C, et al. Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. Eur Heart J 2005;26:667–74.
12. Hausenloy DJ, Yellon DM. Time to take myocardial reperfusion injury seriously. N Engl J Med 2008;359:518–20.
13. Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. J Am Coll Cardiol 2009;54:2145–53.
14. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) Trial. JAMA 2000;284:60–7.

Key Words: ST-segment elevation MI (STEMI) ■ primary PCI ■ facilitated PCI ■ reperfusion therapy ■ fibrinolysis.