EDITORIAL COMMENT

Confusion in Reperfusion*

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In this issue of the Journal, Dubois et al. (1) evaluate the clinical outcomes among patients treated with urgent or elective percutaneous intervention (PCI) after pharmacologic reperfusion with tenecteplase combined with unfractionated heparin, enoxaparin, or abciximab. The data presented here indicate that treatment with the glycoprotein (GP) IIb/IIIa inhibitor abciximab (ReoPro, Centocor Inc., Malvern, Pennsylvania) is associated with poorer clinical outcomes, including a higher mortality rate at one year. These results stand in contrast to studies, such as ADMIRAL, in which clinical benefits were observed with the administration of abciximab in the absence of fibrinolytic agents (2). Such divergent outcomes can at times lead to what I call “confusion in reperfusion.” A careful review of differences in trial design and methodology are needed to reconcile such disparate outcomes across well-designed and well-conducted clinical trials.

The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) authors examined the clinical outcomes among patients treated with PCI after fibrinolytic monotherapy or low-dose fibrinolytic coupled with full-dose abciximab administration. The frequency of urgent PCI in the trial was low (<15%); this is in keeping with the equipoise regarding the clinical benefit of performing PCI shortly after fibrinolytic administration (3–6). Early trials in the era of conventional balloon angioplasty suggested that clinical outcomes were actually poorer among patients treated with rescue or adjunctive PCI after fibrinolysis, largely because of a heightened risk of abrupt closure secondary to hemorrhage into the vasa vasorum of the vessel wall (3,4). However, in the modern era of intracoronary stent placement, thienopyridine, and GP IIb/IIIa inhibitor use, the results may now be different (7–9). It is difficult to answer the question regarding the potential benefit of rescue and adjunctive PCI after fibrinolytic administration because of reluctance on the part of operators to randomize patients to a strategy of observing a closed artery (6). Nonrandomized retrospective data from the era of intracoronary stent placement and modern pharmacologic therapy does suggest a benefit in two-year mortality from either rescue (opening of a closed artery) or adjunctive PCI (mechanical interven-

tion if the artery is patent) (8). A likely mechanism of benefit in these patients appears to be a reduction in reinfarction, which is associated with a doubling in mortality (9). Indeed, it is this risk of reinfarction and the risk of intracranial hemorrhage (ICH) that likely account for differences in mortality between fibrinolytic and primary PCI strategies, particularly because fibrinolytic strategies may achieve patency more rapidly, albeit less fully.

In the ASSENT-3 trial, GP IIb/IIIa inhibition was administered concurrently with half-dose fibrinolysis. The ASSENT-3 data do not address the safety or efficacy of the delayed administration of GP IIb/IIIa inhibition after full-dose fibrinolysis. Although there are no randomized data to address this issue, a recent meta-analysis involving 3,418 patients undergoing adjunctive PCI in the ASSENT-1, -2, and -3, Global Utilization of Strategies To Open occluded arteries (GUSTO)-III and -V, Thrombolysis In Myocardial Infarction (TIMI)-10B and -14, Intravenous nPA for Treatment of Infarcting Myocardium Early (IN-TIME)-2, Strategies for Patency Enhancement in the Emergency Department (SPEED), Fibrinolytic and Aggrastat ST-elevation Resolution Trial (FASTER), Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction (ENTIRE)-TIMI-23, and Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trials was presented at the 2003 American College of Cardiology meeting, and the results are in contrast with those observed in ASSENT3 (10). In this post-hoc, nonrandomized analysis, all patients received full-dose fibrinolytic monotherapy. The risk of moderate bleeding by the GUSTO criteria was increased by 0.6% (7.1% vs. 6.5%, odds ratio [OR] 1.47, 95% confidence interval [CI] 1.07 to 2.02) as was the risk of moderate-to-severe bleeding (14.2% vs. 2.4%, OR 0.16, 95% CI 1.24 to 2.16). The risk of death tended to be lower among patients who underwent PCI within 24 h of presentation who were treated with a GP IIb/IIIa inhibitor (4.6%, n = 1,032 vs. 6.6%, n = 2,386, OR 0.71, 95% CI 0.49 to 1.01). In this meta-analysis, the use of PCI and GP IIb/IIIa inhibitors was not randomized; therefore, unmeasured treatment biases may have again confounded outcomes. In contrast with the ASSENT-3 trial, patients in the meta-analysis received a variety of GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) and a variety of fibrinolytic agents (alteplase, reteplase, and tenecteplase). Obviously, the timing of GP IIb/IIIa inhibition in relation to the fibrinolytic administration may play a role in bleeding complications, and this was not adjusted for in the analysis.

It should also be borne in mind that although currently available fibrinolytic agents all have a relatively short half-life, rt-PA administration, and to a lesser extent nonrecombinant tissue-type plasminogen activator (t-PA) administration, may result in significant fibrinogen depletion that may persist for up to 12 h (11), extending the biologic half-life of the agent and the risk of bleeding. Given the limited data that are available, the risks and benefits in the

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administration of full-dose GP IIb/IIIa inhibition after full-dose fibrinolytic administration must be weighed carefully. Patients who are at high risk of ICH include the elderly, females, patients with low body weights, and hypertensive patients. Consideration should also be given to whether the patient received an agent that depletes fibrinogen, such as r-PA and, to a lesser degree, t-PA. A stat fibrinogen level can be checked to ascertain whether the fibrinogen level is above 100, a threshold below which there are data to suggest an increase in bleeding risk (12). Those patients with limited benefit might include patients who present late with low-risk anatomy, such as hemodynamically stable inferior infarction.

Data from the ASSENT-3 trial also do not address the efficacy of GP IIb/IIIa administration alone before PCI. Administration of abciximab in the cardiac catheterization laboratory was associated with a modest reduction in events in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial (13). It should be noted that not all patients in the CADILLAC trial had ST-segment elevation and that the trial population may have included some lower risk patients, as demonstrated by the 1% to 2% mortality in this trial (13). Earlier administration of abciximab was associated with improved clinical outcomes in the ADMIRAL trial (2), an effect that appeared to be mediated by improved angiographic outcomes. Likewise, angiographic data from the randomized TIGER-PA trial of pre-PCI tirofiban (14) and case-control data from the RAPIER study of eptifibatide (15) indicate that these agents also improve TIMI flow grades, frame counts, and perfusion grades before primary PCI.

The ASSENT-3 authors were careful to control for known confounders and performed a detailed propensity analysis. Despite their careful efforts, unidentified confounders may have influenced the mortality observations. The ASSENT-3 was an open-label trial and PCI was performed at the discretion of the treating physician. Fewer patients who received abciximab underwent urgent PCI, indicating that these were potentially a more select group of patients. It is entirely possible that those patients treated with abciximab were sicker. Chance could also have played a role in the findings given that 46 comparisons were made. Of the 46 comparisons, 3 were positive and 2 of the significant results pertained to increased bleeding, which are biologically plausible findings.

In contrast with the data presented here from the ASSENT-3 study (in which a minority of patients underwent urgent PCI), planned and ongoing trials of facilitated PCI strategies will instead require that all patients undergo PCI (predominantly urgent) after pharmacologic therapy. Mechanical intervention in all patients will greatly reduce the potential selection bias that is inherent to any retrospective analysis. These future trials should provide important prospective randomized data by which to compare the efficacy of a variety of pharmacologic regimens, and hopefully lend some clarity to any ongoing confusion in reperfusion.

REFERENCES