The Safety and Efficacy of Glycoprotein IIb/IIIa Inhibitors for Primary Angioplasty

More Options to Choose and More Time to Decide*

David J. Moliterno, MD, FACC,
Khaled M. Ziada, MD, FACC
Lexington, Kentucky

In this issue of the Journal, Gurm et al. (1) present observational data showing no apparent difference in early outcome among primary percutaneous coronary intervention (PCI) patients receiving the small-molecule platelet glycoprotein (GP) IIb/IIIa inhibitor epifibatide versus those receiving the monoclonal antibody abciximab. Their findings are from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) database, a large regional PCI registry that includes demographic, procedural, and hospital outcome information from several interventional cardiology centers. Importantly, all patients undergoing PCI at these centers are included; the data are prospectively collected; the definitions are standardized, and samples of data are audited for accuracy. Thus, the registry should accurately represent contemporary PCI practice in this region of the U.S.

There is good evidence that abciximab as adjunctive pharmacologic therapy for primary PCI improves outcomes. Several randomized, placebo-controlled trials have consistently demonstrated a 40% to 60% reduction in a 30-day composite ischemic end point (death, myocardial infarction, and urgent target vessel revascularization [TVR]) with abciximab in this setting (2–6). This benefit has been primarily driven by a marked reduction in the rates of infarction and urgent TVR. No individual trial has observed a statistically significant reduction in 30-day mortality. However, a meta-analysis of placebo-controlled abciximab trials for ST-segment elevation myocardial infarction (STEMI) did demonstrate a moderate reduction in mortality at 30 days (2.4% vs. 3.4%, p = 0.047) and at 6 to 12 months (4.4% vs. 6.2%, p = 0.01) among those receiving abciximab during primary angioplasty (7). In a subsequent analysis of this combined dataset, the mortality benefit was shown to be proportional to the baseline risk; the benefit was more robust among higher-risk patients (8) and progressively less evident in lower risk patients (5). Likely for several reasons, including the lack of consistent benefit across patient risk groups and the small sample size of individual trials, the American College of Cardiology/American Heart Association guideline writing committees for the management of STEMI and for PCI issued a Class IIa recommendation (Level of Evidence B) for the use of abciximab in primary PCI (9,10).

Improved outcome with particularly early administration of abciximab (i.e., before-hospital or prior to arrival in the catheterization laboratory) was first suggested by Montalescot et al. (4), was reinforced in subsequent reports (11,12), and seemed intuitive. On the basis of these findings, early administration was emphasized in the guideline recommendations (9,10). Since then, however, the more adequately powered FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) trial (13) (n = 2,452) has shown that early abciximab administration does not reduce ischemic end points when compared with abciximab given immediately before angioplasty. The benefit of abciximab use in primary PCI may also be affected by increased bleeding risk. In the STEMI–abciximab meta-analysis, bleeding complications were higher with abciximab than placebo (5.2% vs. 3.2%; odds ratio [OR] 1.66; 95% confidence interval [CI] 1.47 to 1.88; p < 0.001) for all comers. That difference was attenuated when facilitated PCI trials were excluded and only primary PCI (without fibrinolytic administration) studies were considered (4.7% vs. 4.1%; OR 1.16; 95% CI 0.85 to 1.59; p = 0.36) (7). The FINESSE data show a similar pattern with an increase in major bleeding complications in the abciximab-lytic facilitated-PCI group. The lowest rate of major and minor bleeding in the FINESSE study was in the group receiving abciximab in the catheterization laboratory, thereby putting another dent in the hopes of improved outcomes with early GP IIb/IIIa administration.

Despite limited efficacy data, and mainly because of cost concerns, the small-molecule agents epifibatide and tirofiban are used more commonly than abciximab in the U.S. and Europe, respectively. Two single-center retrospective comparisons of primary PCI patients receiving abciximab or epifibatide (14,15) have suggested similar outcomes for these agents. Likewise, small randomized studies of abciximab versus a higher-dose tirofiban regimen have suggested similar angiographic and clinical outcomes.
(16,17). These limited datasets and the similarity of the mechanism of action with abciximab were credited for giving the small-molecule IIb/IIIa inhibitors a Class IIb recommendation (Level of Evidence C) for use in primary PCI in the recently updated guidelines (10).

So how do the findings of Gurm et al. (1) add to our knowledge of GP IIb/IIIa inhibitors during primary PCI? First, this is the largest prospective registry report of primary PCI patients (>2,800) treated with eptifibatide. Second, their patient population should accurately represent contemporary practice and evidences high-risk features (~25% above the age of 70 years, >50% with an abnormal baseline ejection fraction, and >12% presenting with cardiogenic shock) not seen in many randomized studies. Third, this study confirms the bleeding risk associated with polypharmacy anticoagulation in STEMI. Although bleeding definitions have not been standardized across all trials, blood product transfusion is probably the simplest intertrial metric. In the present report, the transfusion rate of 12% is relatively high (2–6). Likewise, the 8% to 10% occurrence of major adverse cardiovascular events in both groups of the registry is somewhat higher than those reported in the placebo-controlled abciximab trials (2–6). These ischemic and hemorrhagic event rates are a reflection of real-world outcome. Finally, although not adjudicated and examined only to the time of discharge, the specific rates of death, reinfarction, stroke, and TVR were similar in the eptifibatide and abciximab groups.

The authors correctly point out that their findings are not adequate to prove noninferiority of eptifibatide compared with abciximab in primary PCI. That would require a very large and expensive trial, which is unlikely to ever be conducted. But the aggregate evidence for the use of small-molecule GP IIb/IIIa inhibitors in primary PCI is favorable, with no clear disadvantage compared with abciximab. The data of Gurm et al. (1) are probably not enough to upgrade the guideline recommendations for small-molecule IIb/IIIa inhibitors from Class IIb to IIa, but they greatly add to the guideline recommendations for small-molecule IIb/IIIa inhibitors in primary coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293:1759–65.


