The Glycoprotein IIb/IIIa Inhibitor Wars
An Update*

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The use of glycoprotein (GP) IIb/IIIa inhibitors during percutaneous coronary intervention (PCI) has declined in recent years, but 1 of the 3 approved GP IIb/IIIa inhibitors was still used in about 39% of PCI procedures performed during 2008 in the U.S. (Merchant G, personal communication, June 2010). And, GP IIb/IIIa inhibitors remain “big business”: GP IIb/IIIa inhibitor sales were more than $475 million in the U.S. alone in 2008 and much more worldwide (Merchant G, personal communication, June 2010).

Early studies evaluating GP IIb/IIIa inhibitors were among the first to document how frequently small, generally subclinical procedural myocardial infarctions (MIs) occurred during apparently uncomplicated PCI procedures. Empowered by such data, advocates for the widespread use of the drugs successfully changed the lexicon and, in fact, the very definition of procedural MI (1). Whereas the definition of procedural MI had previously required an elevation of total creatine kinase (CK) level, most commonly to twice the upper limit of normal, accompanied by chest pain, electrocardiographic changes, or both, the availability of GP IIb/IIIa inhibitors (which reduce such infarctions by 30% to 40%) empowered advocates for the use of these drugs to change the definition from the previously higher threshold of MI (which occurs in fewer than 1% of patients undergoing PCI) to a 3-fold increase of not CK but CK-MB, which occurs in 4% to 10% of patients undergoing PCI (2). Such infarctions are rarely accompanied by elevations of total CK above normal at all, let alone the development of left ventricular wall motion abnormalities. (They can be seen as “microinfarctions,” however, on magnetic resonance imaging [3]).

While it is not possible to imagine how such small infarctions can be good for a patient, just how bad they are has been the subject of much debate. Further complicating the picture is that several placebo-controlled studies of GP IIb/IIIa inhibitors, and pooled analyses of such trials, have revealed a small (0.4%) but statistically significant absolute reduction in mortality with their use (2). The facts that most deaths in these trials occurred months after a ≤24-h infusion; that most deaths in the placebo arms occurred in patients who had not had procedural MIs; and that no credible mechanism by which these drugs would reduce death months after their use has been widely accepted, let alone confirmed, fanned the flames of controversy (4). Recently, much attention has been focused on the increased risk for bleeding with these drugs, particularly by supporters of bivalirudin, an alternative strategy for preventing procedural complications associated with fewer bleeding complications than GP IIb/IIIa inhibitors.

Public opinion has gradually turned on the importance of small procedural infarctions. The recently approved third-generation thienopyridine prasugrel is better able to reduce procedural infarctions than clopidogrel, the second-generation thienopyridine that is the second-best selling drug in the world, with sales of more than $8 billion per year (5,6). However, the decision to approve prasugrel has been widely criticized because of questions about the significance of such procedural infarctions and because prasugrel, like GP IIb/IIIa inhibitors, increases the frequency of bleeding complications that can occasionally be fatal (6). Nonetheless, the ability to reduce procedural MI so effectively during PCI suggests that GP IIb/IIIa inhibitors will continue to play a role in the future.

There exist 3 different GP IIb/IIIa inhibitors approved for use: abciximab (Eli Lilly & Company, Indianapolis, Indiana), eptifibatide (Schering-Plough, Kenilworth, New Jersey), and tirofiban (Medicure, Winnipeg, Canada). The fierce competition among the companies that make and market these drugs, fighting for their share of the billion-dollar market, has kept the issue of the comparative effectiveness of the GP IIb/IIIa inhibitors in the spotlight. The enormous differences in the price among the 3 agents make the comparative effectiveness and relative costs of these drugs important in this era of health care reform. The average wholesale price of abciximab is $1,836.90 (for a 12-h infusion) and of eptifibatide is $1,121.81 and tirofiban is $711.72 (for 18-h infusions) for an 80-kg patient with normal renal function (Merchant G, personal communication, June 2010). Many argue about whether price ought to be a strong consideration when 2 competing therapies differ in efficacy and safety. If, however, 2 treatments are similar in
efficacy and safety, price is a very important, perhaps the most important, consideration.

Some believe that the primary determinant of the effectiveness of these drugs is their ability to maintain a high level of GP IIb/IIIa receptor occupancy after the initial bolus and throughout the infusion. Interestingly, these drugs were developed so rapidly, with so little phase 1 and 2 study, that the "wrong," or suboptimal, doses for all 3 agents were rushed into clinical practice. Abciximab, first to market, achieves very high levels of receptor occupancy after its bolus, but levels decline during the infusion (7). Declining levels of receptor occupancy during the infusion, allowing up-regulation of unblocked receptors, are believed by some to be a reason that the large, placebo-controlled GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries) trial of abciximab, studying prolonged infusions of the drug, was not only negative but also associated with increasing rates of thrombotic complications with increasing durations of infusion (8). For PCI, eptifibatide was initially studied using a single bolus dose, 135 μg/kg, followed by a 0.5 or 0.75 μg/kg/min infusion, that was also found to be too low (7); the dosing was subsequently greatly increased to a double bolus dose of 180 μg, 10 min apart, followed by a 2.0 μg/kg/min infusion (7). This dose of eptifibatide appears to be the "right" one, leading to high levels of receptor occupancy throughout an 18-h infusion (7). Tirofiban, the only drug whose then owner Merck & Company (Whitehouse Station, New Jersey) was bold enough to perform a head-to-head trial comparing its drug with another, was also found to have too low of an initial bolus (7). Further studies led to an increase in the initial bolus dose of 150%, from 10 to 25 μg/kg (7). With this bolus dose, receptor occupancy is high, and it remains so throughout an 18-h infusion period (7).

Other potentially important differences exist between the drugs than receptor occupancy, however. Abciximab is a large molecule that binds the GP IIb/IIIa receptor with very high affinity (though not irreversibly, as has often been reported) and, unlike the small-molecule agents, also avidly binds the vitronectin (αvβ3) receptor (7). Very little unbound abciximab remains circulating in the bloodstream (7). A transfusion of platelets into a patient on abciximab leads to release of abciximab from native platelet GP IIb/IIIa receptors and transfer to transfused platelets (7). When this occurs, overall receptor occupancy of the entire platelet pool is so low that normal platelet aggregability is restored (7). In contrast, eptifibatide and tirofiban are small molecules, and their administration results in as many as 200 molecules of circulating drug for every molecule that binds to a receptor (7). Therefore, transfused platelets become bound to the circulating unbound GP IIb/IIIa molecules, and platelet transfusions are less able to restore normal platelet function (9). Thus, many believe that eptifibatide and tirofiban are more alike than either is to abciximab. However, tirofiban binds platelet GP IIb/IIIa receptors with great affinity, much like abciximab, in contrast to eptifibatide, whose molecules are frequently releasing and rebinding platelet GP IIb/IIIa receptors, allowing (at least theoretically) fibrinogen molecules to bind GP IIb/IIIa receptors and cross-link with other platelets, the mechanism by which platelet clots form (7). The truth is that while such hypotheses are intellectually stimulating and the fuel for great debates, what really matters is how the drugs perform clinically.

The only large clinical trial comparing 2 agents appropriately sized to detect a difference in a combined end point of death and MI, the TARGET (Do Tirofiban and ReoPre Give Similar Efficacy Trial), revealed that abciximab is superior to tirofiban when the original low, 10-μg bolus dose of tirofiban is used (10). However, because the doses of eptifibatide and tirofiban have been increased, several smaller trials comparing different GP IIb/IIIa inhibitors, including abciximab versus tirofiban and abciximab versus eptifibatide, have been performed, including the EVA-AMI (Eptifibatide Versus Abciximab in Primary PCI for Acute Myocardial Infarction) trial, published in this issue of the Journal (11–14). In this small trial in which 427 patients were enrolled, the primary end point was a surrogate end point, ST-segment resolution. The trial used a noninferiority design with a noninferiority margin of 15%. The investigators concluded that in primary PCI, eptifibatide seems equally effective and safe as abciximab with respect to myocardial reperfusion and clinical events. In reality, the trial was enormously undersized to assess a difference in clinical events (and in fact, there was a sizable difference in mortality and reinfarction between the agents, in opposite directions). This study differs from most in that the eptifibatide infusion continued for 24 h; most have administered it for 16 to 18 h. The impact of this is unknown. Although placebo-controlled trials of eptifibatide in ST-segment elevation MI have been performed, this was the first comparing eptifibatide and abciximab specifically in patients with ST-segment elevation MI. In this issue of the Journal, a talented group of investigators from Sweden analyze their nationwide registry and similarly conclude that the 2 agents, abciximab and eptifibatide, have similar efficacy (15). Well written, and using elegant statistical methodology, the study was carefully done. But many potentially important variables were not known and could not be included in the analysis. And, one should remember the limitations of registries in evaluating the efficacy of drugs. This same registry identified an absolute reduction in mortality of 5.3%, and an adjusted relative reduction in death of 25%, with statins in just the 1 year after a MI, which is not a credible finding (16). Such registry analyses can perhaps provide insight into directionality and proportionality and should be used to generate hypotheses, but they ought not be considered able to provide accurate estimates of real differences between treatments. Interestingly, however, the recent updated ST-segment elevation MI and PCI guidelines judged the totality of evidence to indicate that the 3 GP IIb/IIIa antagonists have similar effectiveness in the setting of primary PCI (17). Although this may be true, we cannot be
certain, and the data ought not be considered convincing or as level 1 evidence.

Based on the 30-day outcomes of patients undergoing primary PCI in recent trials, a trial comparing 2 GP IIb/IIIa agents would need to enroll more than 10,000 patients to show noninferiority of 2 agents if any small but clinically significant margin of noninferiority were used. Such a trial would be so expensive that it is very unlikely one will ever be performed.

What, then, are physicians to do, given the uncertainty about how the 3 GP IIb/IIIa inhibitor drugs compare with one another? No definitive answer can be provided. Some physicians will continue to choose the most studied agents, rejecting undersized trials as inconclusive (which they are). Others are comfortable choosing a promising but less studied agent. Still others will choose the cheapest agent. Still others (unfortunately) choose the agent whose salespeople are most effective, friendly, or attractive (18).

In this era of constrained health care dollars, physicians ought to have all of the evidence they need to make the most informed decisions for their patients. The investigators of both studies are to be congratulated for contributing to the existing body of evidence.

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