Optimal Antiplatelet Therapy During Percutaneous Coronary Interventions Includes Glycoprotein IIb/IIIa Inhibitors

Just Eliminate the Infusion*

Ehtisham Mahmud, MD, FACC, Anand Prasad, MD
La Jolla, California

The benefits of glycoprotein (GP) IIb/IIIa inhibitors are well established for patients with an acute coronary syndrome (ACS) treated with an early invasive strategy, especially in the presence of high-risk features (troponin positivity, ST-segment depression on presentation, recurrent ischemia, or high TIMI [Thrombolysis In Myocardial Infarction] risk score) (1). These benefits exists even in the presence of thienopyridine pre-treatment (2). In contrast, results of studies with and without thienopyridine pre-treatment suggest that the utility of GP IIb/IIIa inhibitors during elective percutaneous coronary intervention (PCI) is limited (3–5).

Regardless of the specific moiety studied (the chimeric antibody abciximab or the small molecules tirofiban or eptifibatide), optimal efficacy of GP IIb/IIIa inhibitors requires a high degree of platelet inhibition during the PCI (6,7). The clinical benefits from potent inhibition of platelet aggregation, specifically the reduction of myocardial infarction (MI), death, and urgent target vessel revascularization, are also accompanied by an increased risk of major and minor bleeding (2–5,8,9). Although a higher risk of bleeding with GP IIb/IIIa inhibitors was observed in all of the clinical trials that established indications for these agents, bleeding was never included as a primary end point in these studies because reduction of ischemic events was thought to be of far greater significance.

The use of a prolonged infusion of GP IIb/IIIa inhibitors (12 h for abciximab and 12 to 18 h for tirofiban/eptifibatide) after successful PCI was also a part of the clinical trial designs used to obtain approval of these agents for clinical use. Although an early study with abciximab and PCI (balloon angioplasty only) suggested that a bolus-only approach with abciximab led to a higher ischemic event rate, this study was performed in the pre-stent era and has never been replicated (10). No subsequent study has adequately supported the need for a prolonged infusion of a GP IIb/IIIa inhibitor after an uncomplicated and successful PCI, especially with routine stenting and thienopyridine pre-treatment.

The REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events–2) trial was a major practice-modifying study in interventional cardiology and led to the widespread adoption of bivalirudin, as opposed to unfractionated heparin with GP IIb/IIIa inhibitor, for non-emergent PCI (11). In this study, 6,010 subjects (86% pre-treated with a thienopyridine) undergoing nonemergent PCI were randomly assigned to bivalirudin (with 7% bailout GP IIb/IIIa inhibitor) versus unfractionated heparin with routine GP IIb/IIIa inhibitor. The study showed noninferiority for ischemic end points of bivalirudin with provisional GP IIb/IIIa blockade, as compared with heparin plus planned GP IIb/IIIa inhibitor, and also demonstrated lower rates of major and minor bleeding with bivalirudin. Importantly, the absence of a major bleed during the index PCI translated to lower 1-year mortality (12). Therefore, this study highlighted the importance of including major bleeding as an important clinical end point, and introduced the concept of a quadruple end point (death, MI, repeat revascularization, and major bleeding) to establish efficacy and safety of antiplatelet/anticoagulant therapy (13).

In this issue of the Journal, Fung et al. (14) present the results of a well-executed study showing that in the absence of certain pre-procedural high-risk features (unprotected left main, ST-segment elevation, MI <48 h, visible thrombus at initial angiography), and in procedural complications (type B or worse coronary dissection, distal embolization, side branch loss, hemodynamic collapse, prolonged ischemia, unsuccessful femoral arteriotomy closure), the optimal use of the GP IIb/IIIa inhibitor eptifibatide during PCI may be as a bolus dose and truncated infusion (~<2 h). The investigators randomly allocated 624 subjects with stable angina or ACS who had undergone successful coronary stenting with eptifibatide to a standard 18-h infusion versus a truncated ~<2–h infusion of the GP IIb/IIIa inhibitor. The 2-h duration of infusion was chosen to allow the antiplatelet effect of a 600 mg bolus dose of clopidogrel in the absence of thienopyridine pre-treatment. This eptifibatide regimen provided the combined benefit of high inhibition of platelet aggregation during the PCI procedure and, with a brief infusion, the potential for a lower risk of bleeding. The incidence of periprocedural myonecrosis as

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Cardiovascular Medicine, University of California, San Diego School of Medicine, La Jolla, California. Dr. Mahmud is on the Speakers’ List and has consulted for Schering-Plough, Eli Lilly, and Sanofi-Aventis.
defined by troponin elevation >0.26 µg/l was similar between the 2 groups (28.3% vs. 30.1%, 18 h vs. <2 h, respectively; p < 0.012 for noninferiority), with similar 30-day rates of death, MI, and target vessel revascularization (p = ns). The incidence of non-Q-wave MI at 30 days was also similar (4.5% vs. 4.8%, 18 h vs. <2 h, respectively; p = 1.0). However, the major bleed rate (REPLACE-2 definition) was higher in the 18-h infusion group (4.2% vs. 1.0%, 18 h vs. <2 h, respectively; p = 0.02). A major limitation of this study is the use of periprocedural troponin elevation as a primary end point, which is not known to be an adverse long-term prognostic factor after PCI. The study is otherwise not powered to adequately address the traditional clinical ischemic end points. However, importantly, this study shows that a brief infusion of eptifibatide is not associated with a higher risk of ischemic events after PCI and results in a lower rate of major bleeding.

Other studies have shown that the evaluation of clinical and procedural angiographic parameters can be used to predict the likelihood of a periprocedural MI after PCI (15,16). In the absence of pre-procedural high-risk characteristics and intraprocedural complications, a prolonged infusion of a GP IIb/IIIa inhibitor or bivalirudin is likely of limited value in reducing the risk of ischemic events, and yet likely to increase the risk of bleeding. Bertrand et al. (17) used the transradial approach with 1,005 patients undergoing PCI and demonstrated noninferiority of abciximab bolus only compared with bolus plus 12-h infusion for both ischemic and bleeding end points. Marmur et al. (18) have reported their retrospective experience with both the eptifibatide and tirofiban bolus-only approach during PCI, obtaining acceptably low ischemic and bleeding event rates with both agents.

The optimal pharmacological antiplatelet regimen to balance ischemic efficacy with the risk of periprocedural bleeding remains in flux. Promising agents in investigational use include the oral P2Y12 antagonists prasugrel and AZD6140, which lead to higher platelet inhibition compared with clopidogrel, and the nonthienopyridine agent cangrelor, a potent intravenous, rapidly acting, and reversible (platelet recovery time 20 to 50 min) P2Y12 receptor antagonist (19). The oral thrombin receptor antagonist TRA-SCH 530348 also results in potent inhibition of platelet aggregation and is in clinical trials. The exact role of these agents and their impact on GP IIb/IIIa inhibitor administration and choice of antithrombin (heparin versus bivalirudin) therapy during PCI remains uncertain.

The results of the BRIEF-PCI (Brief Infusion of Intravenous Eptifibatide Following Successful Percutaneous Coronary Intervention) study by Fung et al. (14) provide fairly convincing evidence that a prolonged infusion of the GP IIb/IIIa inhibitor eptifibatide is likely to be of limited value after a successful and uncomplicated PCI. With the results of this study and currently available data (17,18), the GP IIb/IIIa inhibitor eptifibatide given as a bolus with truncated infusion until the end of the PCI procedure becomes an attractive alternative to bivalirudin for PCI patients. Owing to variability in the platelet reactivity response to clopidogrel, even with thienopyridine pre-treatment, a substantial proportion of patients do not have optimal platelet inhibition during PCI (20). Because ischemic complications of PCI are predominantly a platelet-mediated phenomenon, and pre-procedural clinical or angiographic criteria are imperfect in predicting the likelihood of a periprocedural MI, the bolus dose of eptifibatide can provide maximal degree of platelet inhibition during all PCI procedures regardless of thienopyridine pre-treatment or clopidogrel hyporesponsiveness. Furthermore, as the incidence of a periprocedural MI after a successful and uncomplicated PCI is extremely low, the increased bleeding risk of a prolonged infusion of GP IIb/IIIa inhibitor could be avoided by eliminating the infusion after the PCI procedure.

Reprint requests and correspondence: Dr. Ehtisham Mahmud, Cardiovascular Catheterization Laboratories, UCSD Medical Center, 200 West Arbor Drive, San Diego, California 92103-8784. E-mail: emahmud@ucsd.edu.

REFERENCES

15. Mahmud E, Shaw KD, Penny WF. Patients at low risk for periprocedural myocardial infarction can be identified by assessment imme-

**Key Words:** percutaneous coronary intervention • glycoprotein IIb/IIIa blockade • ischemic complications after PCI • eptifibatide.