EDITORIAL COMMENT

Upstream/Downstream

Glycoprotein IIb/IIIa in Non–ST-Segment Elevation Myocardial Infarction*

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Platelets play a critical role in the atherothrombosis of myocardial infarction (MI). Whether the initial insult is plaque rupture or plaque erosion (1), platelet adhesion with subsequent activation and aggregation is regarded as the next event leading to thrombus formation. If the resultant thrombus is totally occlusive ST-segment elevation myocardial infarction (NSTEMI) is likely to occur, whereas non-occlusive thrombus is likely to lead to NSTEMI/unstable angina (UA). The NSTEMI compromise the vast majority of MI cases, accounting for approximately 1.2 million annual discharges in the U.S. (2). Although the early prognosis is better for NSTEMI, long-term outcomes are similar for both, mainly because of the risk of re-infarction in the patients with NSTEMI.

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Since the identification of the role of platelets in MI, anti-platelet therapy has continued to evolve, with both increasing treatment options and increasing understanding of the various complex pathways involved. Platelets may be activated by a myriad of agonists (thrombin, epinephrine, collagen, thromboxane, serotonin, adenosine-5′-diphosphate, von Willebrand factor, and so on) through various receptors involving complex signaling pathways (3). Platelet aggregation, the occurrence of cross-linking between platelets to form a “white thrombus”, requires the activation of a common final pathway, the glycoprotein (GP) IIb/IIIa receptor-mediated linking of one platelet to another by binding to fibrinogen and in high-shear-stress conditions to von Willebrand factor. Given that platelets may be activated by multiple pathways but aggregate through a single pathway, the GP IIb/IIIa receptor emerged, based on the pioneering work of Coller et al. (4), as an attractive target in the treatment of arterial thrombosis. Glycoprotein IIb/IIIa inhibition has been shown by our group to improve myocardial perfusion in an animal model of ischemia/reperfusion (5), providing mechanistic data for the beneficial effects during percutaneous coronary intervention (PCI) for MI.

Early on, several GP IIb/IIIa inhibitors were developed, notably the monoclonal antibody abciximab and the small molecules tirofiban and eptifibatide. For all three compounds randomized clinical trial evidence has shown reduction in re-infarction rates, and rehospitalization for acute coronary syndrome [CAPTURE (6) with abciximab, PRISM-PLUS (7) with tirofiban, and PURSUIT (8) with eptifibatide] though mortality reductions (particularly at six months or longer) have been less conclusively shown (9). Moreover, the TACTICS-TIMI 18 (10) trial showed that in the presence of anti-IIb/IIIa therapy an invasive approach is preferable in NSTEMI patients and UA patients with ST-segment depressions. Despite class I indication per the American College of Cardiology/American Heart Association guidelines (11) for patients with NSTEMI/UA likely to undergo PCI, the use of GP IIb/IIIa in NSTEMI patients is only 20% (12), and only 12.8% in elderly patients (13). Multiple factors account for this low use: concern over bleeding risk, uncertainty over the best time to initiate therapy (upstream or in the catheterization laboratory), the emergence of the thienopyridines as alternative anti-platelet agents, and the development of direct thrombin inhibitors such as bivalirudin.

In this issue of the Journal, two reports on the use of GP IIb/IIIa in the setting of NSTEMI/UA provide useful information that may help guide clinicians in the use of these agents. The first, the relatively small but well-designed EVEREST (14) trial, randomized patients to upstream versus in-catheterization-laboratory initiation of GP IIb/IIIa antagonists. The upstream arm received the standard dose of tirofiban, as used in the PRISM-PLUS and TACTICS trials. The in-catheterization-laboratory arm received either abciximab or a new higher dose of tirofiban, which has been identified as yielding greater platelet inhibition than the in-catheterization-laboratory dose used in the TARGET trial (15). The results, although preliminary and needing verification in a larger trial, are intriguing. The patients in the upstream arm had better myocardial perfusion both on arrival in the catheterization laboratory and at the end of their procedure, as compared with the higher-dose tirofiban and abciximab patients, who had therapy initiated in the catheterization laboratory. Why might this be so? Why would a lower dose of tirofiban outperform a higher dose initiated during the time of PCI? Although some events do occur upstream while awaiting catheterization, the overall event rate during that waiting period in patients receiving aspirin and antiocoagulation with heparin is low, so that the benefit of GP IIb/IIIa blockers during the upstream time period in absolute terms is small. Rather, the benefit is more likely to occur during and immediately after PCI. Indeed, a previous report in this Journal provided evidence on a mechanistic level that GP IIb/IIIa inhibitors may not only

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prevent thrombus formation (and propagation) but may also lead to dissolution of platelet aggregates already formed in high-shear situations (16), with up to 75% thrombus dissolution. Thus the upstream use of the agent may lead to a lower thrombus load at the start of the procedure, hence less potential for distal embolization during the procedure (17).

The second report (18) in this issue of the Journal addresses the issue of upstream versus in-catheterization-laboratory initiation of GP IIb/IIIa from the cost-effectiveness viewpoint. Using decision analysis methodology, the investigators compared the use of upstream small molecules (tirofiban and eptifibatide) in all comers with NSTEMI/UA (referred to as acute coronary syndrome patients in the study) versus selective in-catheterization-laboratory use with abciximab based on the decision after diagnostic angiography to proceed to PCI. The upstream use of the cheaper small molecules was found to be cost effective in comparison with the use of the more expensive abciximab when the patients were at moderate or high risk as assessed by the Thrombolysis In Myocardial Infarction (TIMI) risk score. Based on the clinical trial data used by the investigators, when the probability of PCI increased to >90%, the use of abciximab was more cost effective. With close to universal use of the more expensive abciximab, the cost effectiveness of the small molecules would only be lost if the actual clinical outcome of abciximab is superior, as indicated by the results of the TARGET trial, which was used for the cost-effectiveness analysis. However, the TARGET trial did not use an upstream approach. If the results of the more relevant EVEREST study are correct, then the advantage of the small molecules, when initiated upstream, would be maintained in all moderate-risk and high-risk patients. The data from the EVEREST trial are also consistent with the low event rate seen in the invasive arm of TACTICS-TIMI 18 (10).

The two studies highlighted above as well as the other data available from clinical trials provide us with better evidence-based management of patients with acute coronary syndrome, whereas certain lingering questions remain:

1) The benefit of potent anti-platelet agents is likely to occur in patients with plaque rupture and superimposed platelet aggregation, and therefore identification of high-risk patients is crucial. Use of GP IIb/IIIa agents in patients with chest pain but without platelet activation (for example because of progression of stable plaque) would not be expected to benefit from GP IIb/IIIa blockers, and may even be harmed. The use of biomarkers such as troponin I (19) (evidence of possible distal embolization) and s-cd40L (evidence of platelet activation) as well as the TIMI risk score, B-type natriuretic peptide, and ST-segment depressions, help in identifying the high-risk patient likely to benefit from upstream use.

2) The increasing use of clopidogrel, particularly with higher-dose loading, has generated data in patients with lower risk (such as elective PCI patients) showing that such therapy may be sufficient (20). Data in high-risk patients, however, still show incremental platelet inhibition with the GP IIb/IIIa antagonists (21).

3) The use of in-laboratory abciximab is still appropriate in patients who have not received a GP IIb/IIIa upstream, and remains the GP IIb/IIIa of choice in STEMI patients treated with primary PCI (should be started prior to arrival in the catheterization laboratory if possible).

4) The use of selective/bailout GP IIb/IIIa blockers in the setting of direct thrombin inhibitors seems promising (22), but requires further validation in larger prospective trials in high-risk patients.

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