“Bolus-only” glycoprotein IIb/IIIa inhibitor use for elective percutaneous coronary intervention: Maybe less is more?

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Rupture of an atherosclerotic coronary arterial plaque, as occurs spontaneously in patients with acute coronary syndromes, or as the result of a percutaneous coronary intervention (PCI), may serve as a stimulus for platelet adhesion, aggregation, and thrombus formation. Resultant platelet-mediated thromboembolic events are believed to cause a large percentage of the non–q-wave myocardial infarctions (MIs), and a rare need for early (<24 hours) repeat target lesion revascularization after PCI.

A number of trials have demonstrated the potential importance of glycoprotein (GP) IIb/IIIa inhibition as a means to reduce the incidence of periprocedural death, myocardial infarction, and target lesion revascularization (MACE) during coronary angioplasty and stenting. Thus, there is a rationale, supported by a significant body of clinical trial data, demonstrating the benefits of GP IIb/IIIa inhibitor use during coronary interventions.

Despite these potential benefits, many interventional cardiologists and hospitals have resisted the routine use of these agents because of the relatively high drug-related costs, concerns about a possible increase in bleeding complications, and skepticism related to a relatively modest absolute reduction of MACE, when compared with unfractionated heparin alone.

The article presented by Marmur et al in the current issue of the Journal suggests that we may be able to improve clinical outcomes, with properly directed and cost-effective use of powerful pharmacologic agents in the cardiac catheterization laboratory. The analysis presented by his group from the original EPIC Trial suggests that there may be significant clinical benefit to a simplified, “bolus-only” regimen of a GP IIb/IIIa receptor blockade, even in relatively high-risk patients.

As pointed out in the article by Marmur et al, there are several caveats to their observations. The EPIC Trial was conducted in an era of primary balloon angioplasty, with the rare use of first-generation stents for abrupt or threatened closure. The primary benefit in this EPIC substudy was a reduction in emergent repeat TLR, rather than a reduction in non–q-wave MI.

The routine use of stent technology, as the primary mode of therapy in PCI, makes some of the observations from EPIC less relevant in today’s world of interventional cardiology. Indeed, the current incidence of urgent repeat intervention after elective stenting is much lower than that observed in the EPIC Trial. The improvement in the incidence of emergent repeat intervention from ~2% to <0.5% is most likely related to both the predictable nature of revascularization results obtained with stents (vs POBA), as well as the routine adoption of high-dose thienopyridine loading, before or immediately after PCI.

Rationale for high-dose single-bolus IIb/IIIa inhibitor use

In today’s world with primary stenting and high-dose pre- or postloading of thienopyridines, the benefits of IIb/IIIa inhibition during PCI are presumably related to an interruption of platelet aggregation that can trigger thromboembolic events, leading to non–q-wave MI during coronary artery manipulation (ie, balloon inflations). Thus, although inhospital abrupt closure is very rare, there is still a rationale for using GP IIb/IIIa inhibitors during coronary stenting to reduce the incidence of non–q-wave MI.

Although there are the limitations of the observations from the EPIC substudy, the concept of using a high-dose, bolus-only IIb/IIIa inhibitor regimen does make sense. The rationale for this approach includes the following: (1) high-dose IIb/IIIa inhibition given as a single bolus has been demonstrated to be very potent in inhibiting platelet aggregation, without evidence of incremental bleeding risk; (2) based upon the pharmacokinetics of eptifibatide or abciximab, one could expect this potent antiplatelet effect to last for at least 2 to 3 hours after a high-dose bolus with eptifibatide, and up to 6 hours with abciximab; (3) the average procedure time for elective stenting in most centers is <1 hour (ie, the actual time that operators are manipulating the
coronary artery and/or rupturing plaque(s) with balloon inflation[s] is relatively short in most cases); (4) with high-pressure stent deployment, followed by high-dose thienopyridine loading, there are very few abrupt closure or acute thrombotic complications that occur after the stent procedure is completed and before hospital discharge; (5) the elimination of the prolonged IIb/IIIa inhibitor infusion may reduce postprocedural bleeding complications (eg, hematomas); and (6) if a high-dose bolus IIb/IIIa receptor regimen could be shown to be equivalent to conventional IIb/IIIa inhibitor regimens (ie, bolus plus drip) in reducing non–q-wave MI, at a fraction of the cost, and with the same or lower bleeding risks, this should encourage the more routine adoption of these agents.

**Clinical outcomes using high-dose bolus IIb/IIIa inhibitors**

Substantial inhibition of the GP IIb/IIIa receptors can be achieved after a large single bolus of commonly used agents such as abciximab or eptifibatide. For example, the level of platelet inhibition after a single 20-mg IV (full vial) bolus of eptifibatide was found to be equivalent to the inhibition reported by the TEAM investigators after 2 weight-adjusted boluses. In an era of high-dose thienopyridine loading, pre- or postprocedure, the inhibition of MACE events may actually be best predicted by the degree of intraprocedural platelet inhibition.

The excellent clinical outcomes in the current EPIC substudy with single-bolus abciximab are consistent with our center’s data using high-dose, single-vial bolus eptifibatide in elective PCI. The results from this registry of 401 consecutive “real-world,” elective stent cases appear to be at least equivalent to the outcomes observed from the ESPRIT trial, using weight-adjusted bolus plus infusion of eptifibatide in elective stenting, or compared with the EPISTENT data, using abciximab. In our registry, using a single vial, bolus only (20 mg bolus eptifibatide), there was a mean of 92% platelet inhibition (Ultegra Rapid Platelet Function Assay, Accutronics, San Diego, CA), yielding only a 1.9% MACE at 30 days. In addition, there was a very low incidence of in-hospital major bleeding complications (0.5%), which compares favorably with data from ESPRIT and REPLACE-2.

**Comparison to direct thrombin inhibitors**

In the REPLACE-2 Trial, bivalirudin, a potent direct thrombin inhibitor, was compared with the IIb/IIIa inhibitor, eptifibatide. Bivalirudin was shown to provide similar protection for periprocedural non–q-wave MI, but with less bleeding risk than eptifibatide. In this study, however, eptifibatide was administered with double bolus, plus prolonged infusion with relatively high-dose, adjunctive, unfractionated heparin.

The adoption of bivalirudin as an alternative to IIb/IIIa inhibitors has been driven by these results along with the appeal of a regimen in which the antithrombotic agent is stopped after the completion of the stenting procedure (ie, no prolonged infusion required). The bivalirudin regimen, in general, is also less expensive than a double-bolus plus infusion using eptifibatide, or bolus plus infusion dosing of abciximab.

A bolus-only technique with IIb/IIIa inhibitors, combined with lower-dose, weight-adjusted unfractionated heparin, may have the same advantages as bivalirudin (ie, reduction in non–q-wave MI, no prolonged infusion, and low bleeding risk), but with even lower costs.

**Cost savings using high-dose, bolus IIb/IIIa inhibitors**

The potential cost savings with bolus-only IIb/IIIa inhibitor regimens should be appealing in this era of tightening hospital budgets and reduced diagnosis-related group reimbursement for PCI. The hospital discounted price of the eptifibatide regimen in the PURSUIT study (bolus plus drip) was $1014. The median cost of the eptifibatide regimen in the ESPRIT study was $502. In contrast, the average cost of a single vial of eptifibatide used in our registry was only $59. Additional cost savings may also be realized, related to the elimination of labor and equipment costs for prolonged intravenous infusions, postprocedure.

**Conclusions**

There is increasing evidence suggesting that we should reexamine the concept of bolus-only GP IIb/IIIa inhibitor use in the setting of elective PCI. The findings from the current reevaluation of the EPIC data, along with the trend toward more aggressive loading of thienopyridine antiplatelet therapy, suggest a need for randomized clinical trials to evaluate this treatment strategy, particularly in a low- to moderate-risk, elective stent population.

**References**

4. PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: