Eptifibatide in Coronary Intervention
Past Time for the Next Chapter

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You can observe a lot just by watching.
—Yogi Berra

A combination of anticoagulant and antiplatelet therapies is foundational to the safe conduct of percutaneous coronary intervention (PCI). This reflects the obligate disruption of coronary vessel integrity and the consequent potential for thrombosis related to PCI. Beginning over 2 decades ago, eptifibatide, an agent that blocks the glycoprotein IIb/IIIa receptor, has been evaluated in clinical trials to ameliorate the potential for PCI-related thrombosis and for improving procedural and clinical outcomes. Although the glycoprotein IIb/IIIa inhibitors have been proven to reduce thrombotic events complicating PCI (death, myocardial infarction, abrupt vessel closure, and stent thrombosis), treatment is accompanied by an increase in the incidence of bleeding events that are in turn associated with worsened cardiovascular outcomes.

The ideal PCI antithrombotic regimen eliminates the potential for catheter and device thrombosis, maximizes the clinical efficacy of the procedure, and minimizes the risk of bleeding. The dramatic evolution in interventional device technologies of the past several decades, coupled with the availability of new antithrombotic agents, has remarkably improved procedure success rates and reduced the potential for PCI-related thrombosis. Nonetheless, the package insert dosing recommendation for eptifibatide has not changed since the registration trials of the 1990s. Several investigators have already explored alternative dosing regimens of eptifibatide to minimize both cost and bleeding risk. However, the efficacy and safety of these novel dosing regimens have yet to be definitively determined, and none of the trials have resulted in changes to the package insert. Considering the permutations of dosing, timing, and duration of not just eptifibatide but also the other antithrombotic adjuncts that can be used during PCI, it is safe to say that the optimal antithrombotic regimen(s) for PCI remains to be identified.

In this issue of Circulation: Cardiovascular Interventions, Gurm et al add to the argument that the package insert dosing regimen of eptifibatide is an anachronism. Gurm et al evaluate the in-hospital outcomes of a large cohort of patients at 47 hospitals treated with eptifibatide as an adjunct to PCI. The analysis was of data provided to the Blue Cross Blue Shield of Michigan Cardiovascular Consortium database. Using comparative effectiveness methodologies (including extensive statistical matching), 21,296 analysis-eligible patients were divided into the 21.2% of patients treated with only a bolus of eptifibatide at the time of PCI and the 78.8% receiving standard therapy (bolus plus any continued infusion after the case). In-hospital clinical outcomes, including mortality, bleeding, transfusion, myocardial infarction, repeat PCI, and stent thrombosis, were determined. The key finding was that patients receiving the bolus only of eptifibatide had significantly lower rates of bleeding events (odds ratio, 0.74 [0.58–0.93]; P=0.014) and blood transfusion (odds ratio, 0.69 [0.52–0.92]; P=0.012) although there were no statistically significant differences in rates of mortality, myocardial infarction, repeat PCI, or stent thrombosis. Equally revealing were the relative rates of the classes of events: bleeding events were the most frequent (n=764), followed by transfusion (n=558), with either of these occurring 6 to 8× more frequently than death and >20 times as frequently as stent thrombosis. This disparity in the frequency of bleeding events versus complications related to thrombosis only serves to underscore the need to more aggressively address the former, with the authors appropriately concluding that a bolus only dosing strategy is supported by their findings.

Gurm et al are to be congratulated for attempting to address this real-world scenario using a comparative effectiveness approach. Identifying the optimal antithrombotic regimen(s) for PCI will likely never be approached via randomized clinical trials given the multiplicity of combinations of agents, dosing, and duration and because the economics and politics do not favor the requisite series of trials. Much like many questions in medicine, however, it seems apparent—and is supported by their data—that it is past time for the next chapter to be written with respect to antithrombotic adjuncts in PCI. Further analysis will need to account for the spectrum of thrombotic risk relative to patient presentation, timing of administration of P2Y12 inhibitors, dosing of anticoagulants, and other variables that could not be accommodated in this study. The authors acknowledged that there was insufficient data in the consortium registry to even determine the duration of eptifibatide dosing or whether eptifibatide was discontinued in the catheterization laboratory because of a bleeding event. These limitations argue for more granular data to be collected at the time of PCI procedures if we are to ever
determine the therapeutic approach with the best balance of efficacy and safety.

Determining the optimal antithrombotic strategy for PCI thus remains elusive. Although the authors have focused on safety and efficacy, there are substantial cost implications related to drug acquisition and administration (and adverse event management) to be considered in the evaluation matrix. Well-done comparative effectiveness analyses of larger registries (with adequate adjustment) are the logical approach to addressing the 90% plus of questions in medicine that cannot or will not be addressed by randomized clinical trials. Ideally, these types of analyses could even lead to changes in the package label such that adjusted dosing regimens (in the case of eptifibatide) would no longer be considered off-label. Although the traditional position is that observational analysis is only hypothesis-generating, one has to question when sufficient change in practice has occurred to abandon previously proven and approved strategies. This construct then allows us to ask the real question: in 2015, what is the optimal antithrombotic regimen(s) in PCI?

Disclosures

None.

References


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