EDITORIAL COMMENT

What Role for Glycoprotein IIb/IIIa Inhibition in Contemporary Coronary Intervention?*

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Improved antithrombotic therapies have remarkably enhanced the safety and efficacy of percutaneous coronary intervention (PCI). Although rates of short-term ischemic complications were as high as 10% to 13% in patients receiving only aspirin and intraprocedural heparin during PCI, addition of platelet glycoprotein IIb/IIIa inhibitors (GPI) reduced that risk by as much as 50% and long-term mortality by nearly 20% (1,2). Intense platelet inhibition produced by these agents, however, resulted in increased rates of bleeding complications (3,4), associated with prolonged hospitalizations, increased costs, and late mortality (5). Nevertheless, GPIs became widely accepted into the standard of care during PCI, especially in the setting of acute coronary syndromes (ACS), where the clinical benefit of these agents seemed particularly noteworthy.

But interventional practice and pharmacotherapies continued to evolve, with development of refined, thinner-strut stent designs associated with less thrombogenicity (6), early administration of platelet ADP P2Y$_{12}$ receptor antagonists to patients with ACS or undergoing PCI (7), and introduction of the more potent P2Y$_{12}$ inhibitors ticagrelor and prasugrel (8,9). In this context, the balance of benefit versus risk with GPI became less clear. In a randomized trial among patients who had received clopidogrel before elective PCI, GPI did not reduce ischemic complications but did increase bleeding (10). Subsequent trials in higher-risk patients with ACS showed efficacy of GPI in reducing ischemic complications of PCI (11), but also showed that these agents could be reserved for selective use in those patients with substantial thrombus burden, high-risk anatomy, or intraprocedural complications (3). A series of trials were then carried out among patients undergoing PCI for elective indications or ACS, demonstrating that substitution of the direct thrombin inhibitor bivalirudin for the combination of heparin plus a GPI consistently reduced bleeding complications by as much as 40% (12-14). Neither ischemic events nor long-term mortality was increased with bivalirudin in those trials, and this agent eventually supplanted heparin and GPI during PCI for many patients.

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In this issue of *JACC: Cardiovascular Interventions*, Safley et al. (15) report the results of an observational study examining the efficacy and safety of GPI in the contemporary interventional management of patients with ACS. They performed a retrospective analysis of data obtained from the National Cardiovascular Data Registry of more than 970,000 patients undergoing PCI for an ACS between 2009 and 2011. Approximately one-third of these patients received GPI, and the association between GPI use and in-hospital mortality and major bleeding was assessed. Three different methods were used to adjust for potential bias in the application of GPI: multivariable logistic regression, propensity matching, and instrumental variable analysis. In the adjusted analyses, GPI use was associated with reduced mortality (relative risk ranging from 0.72 to 0.90) and increased major bleeding (relative risk ranging from 1.53 to 1.93). The authors concluded that "in the modern era of PCI, there may still be a role for judicious use of GPI."

The principal concern with this study, of course, is the observational nature of the analysis. Without randomization, any observed associations between the treatment variable (GPI) and outcome cannot be proven to be causative. Nevertheless, the statistical methods are sophisticated and appropriate, and the authors have extensive experience in rigorous analyses of large-scale databases. That all 3 methods of statistical adjustment resulted in very similar hazard ratios for the mortality and bleeding endpoints suggests that the findings are robust. Thus, although acknowledging that all nonrandomized comparisons seeking to establish causation or outcome with a particular therapy must be considered exploratory, it is reasonable to regard the methodology as valid and the results as likely reflective of outcome of randomized trials.

The results of this study, then, would seem to suggest a remarkable benefit of GPI in patients undergoing PCI for ACS, with 10% to 28% reductions in mortality that would far outweigh in importance the 50% to 90% increases in major bleeding. It is not clear, though, what information this analysis provides beyond that of randomized trials that have already been performed. The authors provide the rationale that randomized trials were powered to show reductions in "myonecrosis rather than mortality" and enrolled "low to moderate risk patients…to limit bleeding complications." Yet pooled analyses of randomized trials have been published with sufficient statistical power to assess mortality (2), and the authors of the current study have provided little information to contrast the risk profile of their patients with those in the large-scale randomized trials.

Moreover, examination of relevant subgroups in this study suggests that the results are largely confirmatory and provide limited new insights into the use of GPI in contemporary practice. Perhaps most importantly, GPI was observed to reduce mortality in patients receiving heparin, but not those treated with bivalirudin. This finding is completely concordant with outcomes of the multiple randomized trials that showed bivalirudin to produce similar ischemic outcomes, including mortality, as does heparin with GPI (12-14). Thus, the current study does not modify or expand the indications for GPI relative to bivalirudin. A puzzling finding of this study is that mortality was reduced by GPI among patients with ST-segment elevation myocardial infarction, but increased in those without ST-segment elevation. This observation lacks biological plausibility and raises concerns regarding unadjusted confounding of these observational data. Finally, the results provide little information regarding 2 important recent advances in interventional practice. Only 5% to 7% of patients in this cohort had radial artery access, and the findings may thus not be reflective of current practice where rates of radial access are substantially higher. Only 11% to 12% of patients received third-generation $P2Y_{12}$ inhibitors, despite the superiority of these agents among patients with ACS (8,9), and results were not reported for this important subgroup. Appropriate utilization of third-generation $P2Y_{12}$ antagonists may well attenuate the incremental benefit of GPI with lower risk of bleeding.

Thus, although one can hardly disagree with the authors' conservative conclusion that there may be a role for "judicious use" of GPI in contemporary coronary intervention, selection of pharmacotherapy must continue to be guided by the findings of the randomized trials. GPI provides superior protection against ischemic events in patients undergoing PCI for ACS, particularly those patients at high risk for ischemic events, when compared with heparin alone with clopidogrel. This benefit was observed in randomized trials published as recently as 2006 (11) and is corroborated by the current observational database analysis. But bleeding is increased with GPI, and alternative approaches exist. There is no advantage of GPI and heparin over bivalirudin, and the latter strategy reduces bleeding. The role of GPI in combination with ticagrelor or prasugrel for ACS remains to be defined.

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