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EDITORIAL COMMENT

Glycoprotein IIb/IIIa Inhibitors

Do They Still Have a Role?*

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Compared with aspirin plus unfractionated heparin, the addition of intravenous glycoprotein IIb/IIIa inhibitors (GPIs) represented a major advance in percutaneous coronary intervention (PCI). The benefits were particularly notable in high-risk patients, such as those with acute coronary syndromes or diabetes (1,2). The potent platelet blockade afforded by these agents consistently reduced periprocedural ischemic complications, including myocardial infarction (MI). Their necessity, however, in the context of stenting with concomitant adenosine diphosphate (ADP) receptor antagonism has been challenged, especially during elective PCI.

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In this issue of the *Journal*, Winchester et al. (3) have performed a rigorous meta-analysis of the available data to address whether GPIs provide incremental benefit during nonurgent PCI in patients receiving stents and ADP blockers. Nonfatal MI at 30 days was reduced from 8.3% to 5.1%. This one-third reduction was highly statistically significant and was similar for abciximab and for small-molecule GPIs. Although one might have hypothesized that the effect would be larger in patients without thienopyridine pre-treatment, no effect modification was noted. Similarly, when year of publication was examined in a meta-regression analysis, the benefit of GPIs was similar in the more recent studies compared with the older studies—in contradistinction to the prevailing sentiment in the clinical community. Thus, compared with heparin, GPIs provide a similar degree of benefit now as they did a decade ago, and the marked drop in their use may not be entirely justified.

The reduction in target vessel revascularization at 30 days in the analysis by Winchester et al. (3) was not significant. The increase in major bleeding was not significant, although the increase in minor bleeding from 1.7% to 3.0% was highly significant. Of note, the definition of minor bleeding that was used included forms of bleeding that many clinicians (and patients) may not deem truly minor in the present era. Thrombocytopenia also was increased significantly with GPIs (particularly abciximab), but reassuringly, the rate of stroke was not significantly higher.

Mortality was examined at 30 days and was not significantly lower in those patients randomized to GPIs; in the subset of patients for whom mortality rates were available at 1 year, the same pattern was seen. Rates of mortality after elective PCI are relatively low, and with a much larger sample of patients, perhaps the observed mortality difference would have become statistically significant. Potentially, longer follow-up would be necessary to see if the reductions in periprocedural MI translated into an impact on left ventricular function or on mortality. Alternatively, the increases in minor bleeding (which, as mentioned above, were not so minor) may have offset to an extent the benefits expected from the decreases in MI. Periprocedural MI as an end point has been controversial (4–6). Uncertainty remains over the exact threshold at which a periprocedural MI "counts," and harder end points such as Q-wave MI and death have not always tracked with periprocedural MI, although this in part may be because of the definition used.

ADP receptor blockade clearly has a profound influence on periprocedural outcomes, and a recent meta-analysis showed that even more potent ADP blockers than standard-dose clopidogrel have further impact (7). Thus, the incremental value of GPIs in the setting of the more potent ADP blocking strategies remains to be determined. Therapies other than conventional antithrombotics, such as statins, have been shown to reduce periprocedural MI, potentially further reducing the impact of GPIs (8,9). However, there is no reason to think that the benefits of statin pretreatment would not be complementary to GPIs.

The emerging data regarding bivalirudin with bailout use of GPIs provide a further challenge to routine use of GPI blockade (10,11). Consistently, bivalirudin has decreased bleeding complications compared with GPIs, while providing slightly less protection against periprocedural MI (12–15). Sophisticated analyses have shown that the impact of significant bleeding at least equals and may surpass that of small periprocedural MIs (16,17). The relationships between bleeding and outcome are similar to those between periprocedural MI and outcome—partially explained by confounding and partially explained by direct causation, with the ratio depending on the magnitude of the event. That is, a large bleed or MI likely can lead to subsequent ischemic events including death, whereas a very small bleed or MI is unlikely to be directly causative. Regardless, the data show that bivalirudin with provisional GPI use compared with routine GPI use is associated with lower mortality at 1 year in acute MI patients undergoing PCI, which is particularly comforting when using bivalirudin in patients

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who are lower on the ischemic risk spectrum, as in elective PCI (18).

Although one could make a cogent argument for substituting bivalirudin routinely for GPIs based on randomized clinical trial and registry data at the current time, the field of GPIs has not remained entirely static, either. Shorter infusions may provide a similar degree of benefit as longer infusions, although further large-scale study is needed (19). Additionally, intracoronary infusion of GPIs (comparative trials of which were excluded from the present meta-analysis) may have greater efficacy and safety compared with intravenous infusion, and this approach currently is being studied (20). Costs also may drop. Radial access decreases the absolute rate of bleeding substantially, allowing more potent antithrombotic strategies to be reconsidered. Thus, in the future, there may yet be a renaissance of GPIs.

The analysis by Winchester et al. reminds us not to discard older drugs simply because they are older. Of course, data continuously need to be reevaluated as additional clinical trial and registry data are published. Nevertheless, this meta-analysis demonstrates that even on a background of aspirin, standard thienopyridine regimens, and heparin—the PCI cocktail most commonly used worldwide—GPIs continue to have an important potential role. Notably, this data set further validates the concept that additional platelet inhibition is warranted beyond that provided by aspirin and standard-dose thienopyridines. Whether this in fact will be GPIs or one of the novel antiplatelet regimens remains to be seen.

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