Will Diabetes Save the Platelet Blockers?

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More than 30,000 patients have been enrolled in trials assessing the efficacy of glycoprotein (GP) IIb/IIIa inhibitors in unstable angina (UA) or non-ST-segment elevation MI (NSTEMI). The initial trials demonstrated that the use of a GP IIb/IIIa inhibitor resulted in a significant decrease in the rate of death or nonfatal myocardial infarction.1,2 More recently, however, the GP IIb/IIIa inhibitor with the best track record to date in the setting of percutaneous coronary intervention (PCI), abciximab, was tested in UA/NSTEMI in the Global Use of Strategies To Open occluded coronary arteries in Acute Coronary Syndromes (GUSTO IV–ACS) trial, which enrolled patients in whom PCI was not intended, and showed no benefit.3 These disappointing results may have been related to issues of dosing, patient selection, and trial design, but nevertheless, they have led to a reappraisal of the utility of GP IIb/IIIa inhibitors in UA/NSTEMI.

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In the present issue of Circulation, Roffi and colleagues4 revive enthusiasm for the use of GP IIb/IIIa inhibitors in acute coronary syndromes (ACS). They wished to determine whether patients presenting with UA/NSTEMI who had diabetes mellitus derived particular benefit from GP IIb/IIIa inhibition. To answer this question, they performed a meta-analysis of the 6 major, placebo-controlled, GP IIb/IIIa inhibitor trials to date. Stratifying by diabetic status, they found that assignment to active treatment with a GP IIb/IIIa inhibitor was associated with a significant 26% reduction in mortality among diabetic patients, whereas there was no effect among nondiabetics. These results were consistent across all 6 trials, despite the use of different GP IIb/IIIa inhibitors.

There is a priori biologic plausibility to support these intriguing results. Not only is diabetes mellitus a well-established risk factor for the development of atherosclerotic coronary artery disease, but compared with their nondiabetic counterparts, diabetic patients have higher morbidity and mortality in the setting of UA/NSTEMI and after PCI and coronary artery bypass grafting. It has been hypothesized that the higher rate of adverse outcomes is due to altered hemostatic factors. To that end, abnormal platelet aggregation was noted in diabetics >25 years ago.5 More recent studies have demonstrated heightened shear-induced platelet adhesion and aggregation ex vivo in blood from diabetics.6 A significant correlation between glucose levels and platelet-dependent thrombosis, even among nondiabetic patients with fasting blood glucose levels in the normal range, has also been reported.7

The biochemical and molecular links between diabetes and altered platelet activation have been explored by several groups. Increased levels of cell surface adhesion molecules, including P-selectin and the GP IIb/IIIa receptor, have been reported in platelets from diabetics.8,9 Interestingly, despite the latter observation, inhibition of platelet aggregation by abciximab seems equally effective in diabetics and nondiabetics.10 Davi and colleagues11 demonstrated enhanced thromboxane biosynthesis in diabetic patients and its reduction in response to tight metabolic control. More recently, this group has also demonstrated that diabetic patients have elevated levels of isoprostanes, which are recently characterized eicosanoids derived from arachidonic acid via nonenzymatic lipid peroxidation.12 These investigators hypothesized that the increased oxidant stress in diabetics might lead to enhanced generation of certain isoprostanes, especially 8-isoprostaglandin F2α, which induces vasoconstriction and platelet activation. They found elevated urinary concentrations of 8-iso-prostaglandin F2α in diabetics and that both improved metabolic control and antioxidant supplementation reduced these concentrations.

Although alterations in platelet function have garnered most of the attention, other hemostatic factors may also underlie the increased thromboembolic complications observed in diabetics. In a nested case-control study from the Quebec Cardiovascular Study cohort, hyperinsulinemia was identified as an independent risk factor for ischemic heart disease among nondiabetics.13 In epidemiological studies, hyperinsulinemia has been shown to be associated with elevated plasminogen activator inhibitor (PAI)-1 levels, impaired fibrinolysis, and myocardial reinfarction.14 In subsequent in vitro experiments, insulin induced PAI-1 gene expression in cultured human hepatocytes, and a combination of insulin and lipids increased circulating PAI-1 levels in humans.15

Despite the appealing putative pathobiology, the meta-analysis presented by Roffi and colleagues4 raises several questions. As they note, this meta-analysis represents a non-prespecified subgroup analysis and, thus, must be considered exploratory. That being said, the P value for the interaction term between treatment status and diabetes achieved statistical significance (P=0.036), the degree of benefit that diabetics enjoyed with GP IIb/IIIa inhibition was similar across all 6 trials, and the absolute number of events (>300 deaths) was relatively high, all of which add strength to their conclusions.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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What is surprising, however, was the lack of a consistent reduction among diabetics in the composite end point of death or nonfatal myocardial infarction in the 6 trials. This was the prespecified primary end point for each of the individual trials. Although the definition of myocardial infarction varied between trials, this should not affect intra-trial observations. Because the primary mechanism underlying the beneficial effect of GP IIb/IIIa inhibition is thought to be a reduction in platelet aggregation, with consequent reductions in recurrent coronary thrombotic occlusion and prevention of platelet microembolization, it would have been expected that prevention of fatal thromboembolic events would be accompanied by a reduction in nonfatal thromboembolic events. Why this was not observed remains unclear.

Another limitation, as Roffi and colleagues acknowledge, is that this was a univariate analysis. Thus, the possibility exists that it is not diabetes per se who experience a significant reduction in mortality when treated with a GP IIb/IIIa inhibitor. Rather, there may be some other characteristic, independently associated with diabetes, that is the true modifier of the treatment effect with a GP IIb/IIIa inhibitor. Among patients with UA/NSTEMI, several other clinical variables have been associated with a marked benefit with GP IIb/IIIa inhibition, including an elevated baseline troponin level and undergoing PCI.

Patients presenting with ACS who have elevated troponin levels typically have 2 to 3 times the rate of death or MI. Except in GUSTO IV-ACS, troponin-positive patients enjoyed a 50% to 80% reduction in death or MI when treated with a GP IIb/IIIa inhibitor, whereas troponin-negative patients had similar event rates regardless of treatment. It would be of interest to determine the independent effects of diabetes mellitus and troponin status on the degree of benefit associated with GP IIb/IIIa inhibition in these ACS trials.

With regard to PCI, the authors performed further analyses in which they subdivided the diabetic cohort into those who underwent PCI and those who did not. They found that the beneficial effect of GP IIb/IIIa inhibition was even more marked in diabetics undergoing PCI and, by extension, less marked in diabetics who did not undergo PCI. These results need to be viewed cautiously because they represent a subgroup analysis of a subgroup and the total number of events in the PCI subgroup is quite small (∼30 deaths). Nonetheless, these findings are in agreement with the results from a prior meta-analysis by this same group that showed a large benefit of GP IIb/IIIa inhibition in diabetic patients undergoing PCI. Along those lines, no data were presented on whether GP IIb/IIIa inhibitors had any effect on revascularization rates. It would be informative to determine if GP IIb/IIIa inhibitors affect the long-term need for revascularization in diabetics presenting with ACS.

If the benefit of GP IIb/IIIa inhibition truly is related to diabetes, then the next question is, what kind of diabetes? Type I diabetes is an autoimmune disorder, whereas the much more common type II diabetes is due to varying combinations of insulin resistance, β-cell dysfunction, and increased hepatic glucose production. The distinction between type I and type II is rarely made when gathering baseline data in ACS trials. Thus, given their relative prevalences, the majority of the effect seen in this study was likely measured in type II diabetics.

Distinguishing what type of diabetes may be important, depending on the underlying pathobiology. If the benefit of GP IIb/IIIa inhibition is related primarily to hyperinsulinemia and elevated PAI-1 levels, rather than hyperglycemia and heightened platelet activation, then these benefits may not extend to type I diabetics. Of note, the authors did perform stratified analyses based on the type of diabetes treatment and found the same mortality benefit in diet-controlled diabetics and those who used oral hypoglycemics versus those who used insulin. However, the majority of these patients were likely to be type II diabetics taking insulin rather than type I diabetics. Attempting to correlate the degree of benefit of GP IIb/IIIa inhibition with fasting glucose, hemoglobin A1c, or endogenous insulin levels might yield important pathophysiological insights.

The results reported by Roffi and colleagues potentially have implications for more than just the 22% of their ACS population with overt diabetes mellitus. A much larger number of patients have impaired glucose tolerance after an oral glucose load. Although less than one-third of these individuals will go on to develop frank diabetes with fasting hyperglycemia, there are data to suggest that they are still at risk for abnormalities in platelet function. There is also the “metabolic syndrome,” a constellation of central obesity, hypertension, insulin resistance, and hypertriglyceridemia. These patients also have evidence for impaired fibronlysis. Whether GP IIb/IIIa inhibitors would be of particular benefit in these patients remains unexplored, but it is plausible given the observed hemostatic abnormalities.

Two years ago, an editorial in this journal by King and Mahmud was entitled “Will Blocking the Platelet Save the Diabetic?” With the recent results of GUSTO IV-ACS, the proper role of GP IIb/IIIa inhibitors in the management of patients with UA/NSTEMI not undergoing PCI is less clear. Thus, the striking mortality benefits in diabetics identified by Roffi and colleagues may wind up saving the platelet blockers.

What about nondiabetics? It would be premature to deny them GP IIb/IIIa inhibitors on the basis of the analysis by Roffi et al. Nondiabetics constitute a large and no doubt heterogeneous cohort of patients presenting with ACS. Risk stratification based on only one variable, although convenient, may not be optimal. A combination of clinical characteristics, electrocardiographic changes, and biomarkers may yield more comprehensive and accurate risk stratification and may identify nondiabetics who derive important benefits when treated with a GP IIb/IIIa inhibitor.

Adding a layer of complexity are the data from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, which showed that the use of a different type of antiplatelet agent, the ADP-blocker clopidogrel, led to a reduction in death, myocardial infarction, or stroke in patients with UA/NSTEMI, irrespective of their diabetes status. As antiplatelet therapeutic options expand, our goal should now be to identify the appropriate subsets of patients who will derive the greatest benefit from each of these therapies.
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References

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