Will Blocking the Platelet Save the Diabetic?

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Diabetic patients with atherosclerotic heart disease are more likely to develop complications, whether treated medically, surgically, or with interventional techniques. Among the risks diabetics face is an apparent increase in restenosis after coronary stenting. This issue is addressed in this issue of Circulation by Marso et al. They suggest that although use of the IIb/IIIa antibody fragment abciximab will not solve the restenosis problem for patients undergoing balloon angioplasty or for patients without diabetes mellitus undergoing stenting, its use does in fact reduce the indices of restenosis in diabetic patients undergoing stenting. This finding, if corroborated, will have a significant impact on the medical care of diabetic patients.

In recent years, enthusiasm for performing interventional procedures in patients with diabetes has decreased, especially if those patients have multivessel disease. The National Heart, Lung, and Blood Institute–sponsored multicenter randomized trial comparing coronary angioplasty with bypass surgery (the Bypass Angioplasty Revascularization Investigation [BARI]) clearly demonstrated that patients randomized to surgery had a superior survival rate at 5 years compared with patients randomized to angioplasty. The Emory Angioplasty vs Surgery Trial, which initially showed no difference in a smaller cohort, now at 8 years shows the same trend as the BARI trial. Analysis of the survival curves in these trials leads to the conclusion that much more than simply early restenosis after angioplasty is responsible for this difference. Events continue to occur over many years, undoubtedly reflecting the development and progression of new lesions. Diabetic patients followed up in observational databases also had reduced survival after interventional procedures. This difference is much weaker than in the randomized trials but is borne out in the BARI registry and in a large database from Emory University Hospital.

Most of these trials and the observational studies were performed with balloon angioplasty as the predominant interventional technique. Currently, tremendous enthusiasm exists for the use of stents during percutaneous coronary interventions, especially in large vessels. Will the outcome of diabetic patients undergoing stenting be significantly different from the previous balloon angioplasty experience? Because stents have been shown to reduce the restenosis rate in many patients, will this translate into improved clinical outcomes for diabetic patients undergoing stenting as well? Observational studies send mixed signals regarding restenosis after stenting in diabetic patients. Recently, Van Belle et al challenged the original observation of Carozza et al that suggested that diabetic patients had a much higher restenosis rate after stenting. In this more recent observation, the restenosis rate was 25% among diabetic patients and 27% among nondiabetic patients. There are recent data to support the notion that compared with angioplasty alone, intracoronary stents have decreased the rate of restenosis in diabetics. Until this EPISTENT substudy, there have been no prospective large-group comparisons of diabetics and nondiabetics undergoing stenting.

The EPISTENT study set out to establish whether the addition of abciximab could significantly improve the outcomes of patients undergoing coronary stenting and also compared coronary stenting with abciximab to balloon angioplasty with abciximab. The overall findings of the study have been consistent with previous studies of IIb/IIIa receptor blockers and balloon angioplasty intervention trials. They have shown a marked decrease in acute events, largely non–Q-wave myocardial infarction and urgent revascularization. However, there have not been significant differences in late events, which suggests a neutral effect on restenosis.

This substudy of the diabetic population of EPISTENT provides 2 findings that are not surprising and 1 finding that is quite surprising. First of all, the end point of death was very low in both groups to 6 months and was not significantly different. Second, the reduction in myocardial infarction occurred primarily in the postprocedure period, and the 6-month reduction in myocardial infarction was entirely accounted for by the early differences. This finding is consistent with the main study and reflects the impact of the IIb/IIIa inhibitor on acute thrombotic macrovascular and perhaps microvascular events.

The surprising finding is the difference in target-vessel revascularization (TVR). The TVR can be considered a surrogate for restenosis, because only ~33% of the patients were included in the angiographic restudy arm. Among the diabetic patients, as contrasted with the main study, TVR was reduced only in those patients who received both stent and abciximab. Although the number of diabetic patients was not large (just over 150 patients in each group), the TVR rate of patients who received a stent plus abciximab was approximately half the rate for the stent-plus-placebo group. In addition, a small substudy of patients who underwent angiography was also accomplished, and the angiographic loss in

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lumen diameter was 0.21 mm less in the stent-abciximab group than in the stent-placebo group.

Although no argument exists regarding the ability of \( \text{IIb/IIIa} \) inhibitors to reduce indices of acute thrombotic events, this suggestion of a reduction in restenosis is indeed surprising, because this had not been demonstrated previously in balloon angioplasty trials. What could be the explanation for the significantly improved TVR rate? Because there was an early separation in the TVR rate in favor of the stent-abciximab group, one can speculate whether some of the effect was due to acute thrombotic events driving the TVR. In addition, the difference in event rates remained relatively constant to \( \approx 150 \) days. After 150 days, there were no more events in the stent-abciximab group; however, events continued to occur in the stent-placebo group. One wonders what the 1-year TVR rates were and whether they remained different. Once again, the acute results suggest that a significant amount of the TVR may be due to early thrombotic events, and the lack of events in the treatment group after 150 days remains unexplained. The excess TVR in the stent-placebo group after 150 days suggests a response to follow-up angiographic findings. In addition, as the authors point out, more vein grafts were treated in the stent-placebo group.

In the present report, Marso et al\(^1\) report increased 6-month TVR in insulin-resistant versus non–insulin-resistant patients. However, there were no systematic measurements of glucose metabolism in either group. In point of fact, the comparison was between hypertensive, obese, diabetic patients and nonhypertensive, nonobese, nondiabetic patients. It will be interesting to compare diabetics with and without insulin resistance in future trials.

Is there other substantiating evidence that clinical outcome is improved in diabetic patients who are treated with \( \text{IIb/IIIa} \) inhibitors? Tirofiban, a synthetic \( \text{IIb/IIIa} \) inhibitor, was used in the setting of unstable angina and non–Q-wave myocardial infarction in the PRISM-PLUS trial (Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms) and demonstrated a sustained 42\% reduction in myocardial infarction and death at 6 months in the diabetic population (personal oral communication, Pierre Theroux, MD, August 1999). This effect was predominantly due to a reduction in early acute thrombotic events, ie, non–Q-wave myocardial infarction. The subset of diabetic patients who received stents in that study was too small to arrive at a meaningful conclusion regarding the impact of tirofiban on late clinical events or TVR with stenting. Furthermore, no systematic angiographic follow-up was done as a part of that trial.

The issue of angiographic differences at follow-up in the EPISTENT substudy is very interesting, but the numbers are quite small. Total occlusions resulting from early acute thrombotic events in the stent-placebo group, if present, could account for the difference in the late loss index between the stent-placebo and stent-abciximab groups. Another feature that might influence the late loss and late loss index difference is the difference in restudy rate between the stent-placebo and stent-abciximab group. There were 46 stent-placebo patients, and 13 were not restudied, yielding a 72\% restudy rate. There were 46 stent-abciximab patients, and 6 were not restudied, yielding an 87\% restudy rate. In restenosis trials, the less complete the angiographic follow-up, the more severe the restenosis rate. This is because more symptomatic patients and fewer asymptomatic patients tend to be restudied. If this mechanism were operative, then the stent-placebo patients with a lower restudy rate could have had an artificially inflated restenosis manifestation. Weintraub et al\(^14\) found that patients undergoing balloon angioplasty without clinical restenosis actually had a 30\% restenosis rate by angiography. This was compared with patients with clinical signs of restenosis, who had an 87\% restenosis rate. The numbers for stenting would be expected to be smaller, but the same trend would probably apply.

In the ERASER trial (Evaluation of ReoPro And Stenting to Eliminate Restenosis),\(^15\) no significant difference in neointimal proliferation was seen by intravascular ultrasound in patients treated with abciximab at the time of coronary stenting. There were only 19 diabetic patients in ERASER, and the volume of obstructing tissue was found to be 35\% in the diabetic placebo group, 27\% in the diabetic abciximab 12-hour-infusion group, and 31\% in the diabetic abciximab 24-hour-infusion group. All of these were somewhat higher than in the nondiabetic group, which had a 24\% volume of obstructing tissue. If this ultrasound observation holds true in larger numbers, it would suggest that diabetics do indeed have more neointimal proliferation than nondiabetics, but it would leave some doubt as to whether there is a true impact of abciximab. The effect, at least in this small series, seems modest at best. If abciximab reduces the presence of obstructive tissue within stents, what could be the explanations?

1. Prevention of acute thrombotic events that result in total occlusion could skew the follow-up angiographic findings to favor the conclusion that neointimal proliferation was prevented with the use of abciximab. This is not to suggest that prevention of acute occlusion is not a beneficial effect, but if present, it would cast doubt on the function of abciximab in reducing neointimal proliferation.

2. There could be a reduction in persistent nonocclusive thrombus, which could influence the amount of neointimal tissue at follow-up or, by the mechanism of \( \alpha, \beta_3 \) receptor blockade, inhibit neointimal proliferation, migration, and extracellular matrix production.

These mechanisms would be thought to be present in nondiabetics as well as diabetics, so the question remains: if there is a suppression of neointimal proliferation, why is it inhibited in diabetic patients and not in nondiabetic patients?

The mechanism by which vascular disease progresses in diabetics is a subject of great debate. Serum glucose was not found to predict the presence of coronary disease in an epidemiological study;\(^16\) however, there does seem to be a clear relationship between hemoglobin \( A_1c \) levels and cardiovascular events and survival.\(^17\) If hyperglycemia is important etiologically, there are a number of potential reasons, including cytotoxicity, increased matrix production, and endothelial dysfunction. In addition, the role of oxidative stress in hyperglycemia has attracted increasing attention. Recently, Davi et al\(^18\) explored the implications of lipid peroxidation and increased production of \( \text{F}_2 \) isoprostanes in diabetics.
These substances have been found to be significantly higher in the plasma and urine of diabetic patients and to amplify agonist-induced platelet aggregation. In addition, the oxidation of amino groups by glucose ultimately results in the formation of advanced glycation end products (AGEs) that enhance the aggregation of human platelets ex vivo. Thus, it is possible that the platelets of diabetic patients have an increased propensity toward aggregation and formation of “white thrombus.” These platelets are then most likely to be inhibited by a potent antiplatelet agent that acts at the glycoprotein IIb/IIIa receptor.

However, despite these possible mechanisms of platelet activation in diabetics, Keaney and Loscalzo point out that the evidence for increased lipid peroxidation in diabetics is not firmly established. Clearly, additional investigation is required to better understand the neointimal response in diabetics after coronary stenting. Of greater interest to clinicians is the question of whether IIb/IIIa receptor blockers should be used routinely to reduce restenosis after stenting in diabetics. The ongoing trials testing eptifibatide and tirofiban in stented patients may provide additional insights regarding this important question. The current EPISTENT substudy is the most extensive evaluation of stenting and IIb/IIIa blockade in diabetics, but the results must be confirmed before sweeping changes in clinical practice are made.

References

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