Diabetes mellitus is associated with inferior outcome after percutaneous coronary intervention (PCI). Platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibition is an important adjunctive therapy during PCI and may be particularly so in patients with diabetes mellitus. Platelet GP IIb/IIIa inhibitors are potent antithrombotic agents, and in several large-scale clinical trials with balloon angioplasty and coronary stenting, these agents have produced a consistent and marked reduction in both 30-day ischemic events and long-term (up to 1 to 3 years) mortality. In most cases, a greater magnitude of survival benefit with abciximab has been observed in patients with diabetes as compared with patients without diabetes. Furthermore, clinical risk stratification with diabetes and other variables reliably predicts abciximab benefit for late survival, thereby validating the important mortality benefits (nearly 3 lives saved per 100 patients treated) with abciximab use in high-risk patients during PCI. This large body of evidence has led to the widespread acceptance of platelet GP IIb/IIIa inhibitors to neutralize the excessive mortality associated with PCI among patients with diabetes as compared with patients without diabetes.

See p 3627

The introduction of clopidogrel has changed the landscape of clinical outcomes in PCI. In patients with diabetes, clopidogrel has been shown to be superior to aspirin in reducing recurrent ischemic events. The use of preprocedural clopidogrel can attenuate the increase in C-reactive protein and other inflammatory markers after PCI, even in the presence of abciximab. Pretreatment with clopidogrel (300 to 600 mg) has been suggested to reduce ischemic events during PCI, and long-term (1 year) clopidogrel therapy has been shown to reduce long-term clinical events. Recently, the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics?) study found no benefit with abciximab therapy versus placebo in low- and intermediate-risk patients undergoing PCI who received high-dose pretreatment clopidogrel (600 mg loading dose of clopidogrel at least 2 hours before the procedure). Notably, patients under medical treatment for diabetes were excluded from enrollment in the ISAR-REACT study because of previous data suggesting enhanced mortality benefit with abciximab in patients with diabetes undergoing PCI.

In this issue of Circulation, Mehilli and colleagues report intriguing results from the ISAR-SWEET (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetes?) study. Using the same protocol as in ISAR-REACT, they gave 701 patients with diabetes a 600-mg bolus dose of clopidogrel at least 2 hours before PCI, and the patients were randomized to receive either abciximab or placebo during PCI, followed by at least 6 months of clopidogrel after PCI. Abciximab did not reduce the primary end point of death and myocardial infarction (MI) over placebo (8.3% versus 8.6%, respectively, P=0.91) at 1-year follow-up. The study did show a significant reduction in the incidence of target vessel revascularization (TVR) in the abciximab group as compared with the placebo group (23.2% versus 30.4%, respectively, P=0.03) by 1 year. This reduction in the revascularization rate was consistent with the lower incidence of binary angiographic restenosis in the abciximab group as compared with the placebo group (28.9% versus 37.8%, respectively, P=0.01) at follow-up angiography.

How do we put these data in context with the large body of evidence about abciximab use during PCI in patients with diabetes? The discrepancies in event rates in the cohorts with diabetes between the ISAR-SWEET study and previous studies were apparent. In the pooled analysis of the EPIC (Evaluation of c7E3 Fab for Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade), and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) trials of 1462 patients with diabetes, abciximab treatment reduced the 1-year all-cause mortality rate from 4.5% to 2.5% (P=0.033) and reduced the 1-year MI rate from 11.6% to 6.0% (P=0.022). In contrast, in the ISAR-SWEET trial, the 1-year mortality rates remained higher than previously reported—4.8% in the abciximab group and 5.1% in the placebo group (P=0.86)—perhaps because of the older age and higher prevalence of multivessel coronary disease in the study population. The 1-year MI rates in ISAR-SWEET (4.8% in the abciximab group and 4.3% in the placebo group, P=0.72) were far lower than previously reported in the pooled analysis, however. This reduction in long-term MI...
incidence may have resulted from long-term clopidogrel therapy, in concordance with previous studies.10

To the credit of the investigators, the majority of patients in the ISAR-SWEET trial were discharged on not only aspirin (98%) and clopidogrel (100%), but also on angiotensin-converting enzyme inhibitors (90% to 91%), β-blockers (93% to 94%), and statins (86% to 88%), drugs that have been consistently shown to improve survival and reduce ischemic events in patients with coronary artery disease. Moreover, improvements in pharmacotherapy for diabetes mellitus, such as thiazolidinediones, may suppress markers of inflammatory responses13 and reduce restenosis rates,14,15 further improving overall long-term survival in patients with diabetes. Therefore, intensification of these adjunctive therapies also may have narrowed the differences in long-term clinical outcomes seen in previous studies.

Early (within 48 hours) postprocedural MI accounts for only a small proportion (18%) of the observed mortality benefit of abciximab at 1 year.16 Several studies have suggested that the early rise in systemic markers of inflammation after angioplasty can be diminished by abciximab use.17,18 The recent demonstration of augmented platelet inhibition of fibrinogen binding via lower glycation of platelet membrane proteins by GP IIb/IIIa inhibitors in patients with diabetes also supports this concept.19 Given that some researchers have speculated that part of the long-term benefit of abciximab may come from its antiinflammatory effects, the potential antiinflammatory actions of treatment with clopidogrel may be particularly relevant among patients with diabetes undergoing PCI, further reducing a discernible treatment effect of abciximab.

It is important to recognize that the findings of ISAR-SWEET should not be viewed as definitively excluding a beneficial effect of abciximab in this population of patients with diabetes, particularly given the large previous dataset that linked abciximab with reduction in mortality. This trial was statistically powered for a combined end point of death and MI and a 50% risk reduction. Because the actual primary end point event rate of 8.4% was lower than expected (14%), Mehilli and colleagues estimate that they had only a 69% power to detect 50% risk reduction.12 The statistical power to detect a mortality reduction is even less than that for the composite end point. Although the authors did not provide the odds ratio for mortality based on time-to-event analysis, we can estimate from $\chi^2$ statistics a mortality odds ratio for the treatment effect of abciximab in the ISAR-SWEET study of 0.93 with a 95% confidence interval of 0.5 to 1.9. In other words, these data cannot exclude as much as a 50% decrease (or, alternatively, a 90% increase) in mortality with abciximab therapy. Therefore, the sample size limitations, which have been described for the composite primary end point in the article, are particularly relevant for the more important end point for abciximab therapy in people with diabetes—mortality.

The observation that abciximab was associated with a reduction in angiographic restenosis rates and TVR versus the lack of mortality reduction is an unexpected finding in the ISAR-SWEET study. Typically and consistently, the risk of TVR and angiographic restenosis is found to be higher in people with diabetes as compared with people without diabetes after PCI, but the influence of abciximab on 6-month rates of TVR varied considerably in previous studies. In previous placebo-controlled trials of abciximab during coronary intervention, GP IIb/IIIa blockade was found to reduce TVR rates after balloon angioplasty in patients without diabetes only in the EPIC trial,20 to have no influence on TVR in patients with or without diabetes after balloon angioplasty in EPILOG,21 or to reduce TVR and angiographic restenosis in patients with diabetes only after stenting in the EPISTENT5,22 and ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up) trials.23 Because of these inconsistent results, most cardiologists do not consider an antirestenotic effect to be a compelling reason to use abciximab during PCI. The significant reduction in angiographic restenosis and TVR in ISAR-SWEET is interesting and raises the question of whether abciximab acts on clopidogrel-independent mechanisms in suppressing neointimal hyperplasia. Two potential examples of such mechanisms suggested by the authors include antiinflammatory effects on leukocyte Mac-124 and antiproliferative effects on the vitronectin receptor on platelets and smooth muscles.25 Although this may be a something of a moot point given the broad use of drug-eluting stents, pharmacological suppression of restenosis may still be valuable because TVR and restenosis rates remain higher in patients with diabetes even when drug-eluting stents are used.26

The results of ISAR-SWEET are certainly provocative. It is conceivable that with the current excellent pharmacotherapy, including pretreatment and prolonged postprocedural therapy with clopidogrel, overall lower rates of ischemic events may undermine the benefits of abciximab in selected patients with diabetes. On the other hand, with the large body of evidence from clinical trials conducted before the ISAR-SWEET trial, it remains difficult to dismiss what has been a compelling argument for late mortality benefit of GP IIb/IIIa inhibitors in patients with diabetes or other high-risk patients undergoing PCI.6 Whether we can continue to generalize this concept of a diminished mortality benefit of abciximab in a broad PCI population with diabetes remains unclear. Unless future studies confirmed a lack of efficacy with abciximab with current interventional practice, we believe that the potential benefits of abciximab should not be withheld from patients at high risk, with or without diabetes, for late mortality. Intriguing observations in restenosis reduction in ISAR-SWEET also may generate further interest in the exploration of platelet-dependent or platelet-independent mechanisms of preventing long-term restenosis in patients with diabetes mellitus.

Disclosure

Dr Lincoff has received research support from Eli Lilly and Centocor. Dr Tang is a consultant for Takeda, GlaxoSmithKline, and Amylin Pharmaceuticals.

References


Key Words: Editorials diabetes mellitus coronary disease revascularization platelet-derived factors
Diabetes, Coronary Intervention, and Platelet Glycoprotein IIb/IIIa Blockade: The Triad Revisited
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Circulation. 2004;110:3618-3620
doi: 10.1161/01.CIR.0000151355.07568.B4
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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