Abciximab Reduces Mortality in Diabetics Following Percutaneous Coronary Intervention
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OBJECTIVES
We sought to determine whether abciximab therapy at the time of percutaneous coronary intervention (PCI) would favorably affect one-year mortality in patients with diabetes.

BACKGROUND
Diabetics are known to have increased late mortality following PCI.

METHODS
Data from three placebo-controlled trials of PCI, EPIC, EPILOG, and EPISTENT, were pooled. The one-year mortality rate for patients with a clinical diagnosis of diabetes mellitus was compared with the rate for nondiabetic patients treated with either abciximab or placebo.

RESULTS
In the 1,462 diabetic patients, abciximab decreased the mortality from 4.5% to 2.5%, p = 0.031, and in the 5,072 nondiabetic patients, from 2.6% to 1.9%, p = 0.099. In patients with the clinical syndrome of insulin resistance—defined as diabetes, hypertension, and obesity—mortality was reduced by abciximab treatment from 5.1% to 2.3%, p = 0.044. The beneficial reduction in mortality with abciximab use in diabetics classified as insulin-requiring was from 8.1% to 4.2%, p = 0.073. Mortality in diabetics who underwent multivessel intervention was reduced from 7.7% to 0.9% with use of abciximab, p = 0.018. In a Cox proportional hazards survival model, the risk ratio for mortality with abciximab use compared with placebo was 0.642 (95% confidence interval 0.458–0.900, p = 0.010).

CONCLUSIONS
Abciximab decreases the mortality of diabetic patients to the level of placebo-treated nondiabetic patients. This beneficial effect is noteworthy in those diabetic patients who are also hypertensive and obese and in diabetics undergoing multivessel intervention. Besides its potential role in reducing repeat intervention for stented diabetic patients, abciximab therapy should be strongly considered in diabetic patients undergoing PCI to improve their survival.
Prevention of Ischemic Complications (EPIC) (33); Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) (25); and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) (34).

METHODS

Patient population. Details of the three individual trials have been provided elsewhere. Informed consent was obtained for all patients enrolled. In brief, the EPIC trial consisted of 2,099 patients undergoing high-risk angioplasty in the setting of severe unstable angina, evolving acute myocardial infarction (MI), or high-risk coronary morphological characteristics (33). Patients were randomized to receive a bolus of abciximab, bolus and infusion of abciximab, or placebo. The EPILOG trial consisted of 2,792 patients undergoing either elective or urgent coronary intervention (25). Patients were randomized to placebo, abciximab plus standard-dose, weight-adjusted heparin, or abciximab plus low-dose, weight-adjusted heparin. The EPISTENT trial included 2,399 patients suitable for either balloon angioplasty or stenting for elective or urgent indications (34). Patients were randomized to receive stenting plus placebo, stenting plus abciximab, or balloon angioplasty plus abciximab.

Dosing of abciximab. The dose of abciximab used in the EPIC trial was a 0.25 mg/kg bolus given 10 to 30 min before the procedure and a 10 µg/min infusion continued for 12 h after the procedure. Both the EPILOG and EPISTENT studies used a 0.25 mg/kg bolus 10 to 60 min before the start of the procedure, followed by a 0.125 µg/kg/min infusion (to a maximum dose of 10 µg/min) for 12 h postprocedure.

Study design. Placebo groups and abciximab bolus and infusion groups of the three different trials were pooled. Patients in the arm of the EPIC trial who received the abciximab bolus only, a regimen not found to be clinically effective in reducing ischemic complications, were excluded from the analysis. The classification of patients as diabetic varied among the three trials’ case report forms. In the EPIC trial, patients were classified as diabetic if they had a history of diabetes. They were further classified as insulin-requiring if insulin was listed among their medications. In the EPILOG trial, patients were classified by history of either non-insulin-dependent diabetes or insulin-dependent diabetes. In the EPISTENT trial, patients were classified as diabetic based on history. If they were on an oral hypoglycemic or insulin therapy at the time of hospital admission, this was also recorded. Elevated body mass index (BMI) was defined as greater than 27 kg/m² in women and greater than 28 kg/m² in men (35). Patients were categorized as having the clinical syndrome of insulin resistance if they were diabetic, hypertensive, and obese (elevated BMI) (36).

All trials defined MI similarly, except for minor variations to account for enrollment of patients with ongoing MI. Either new significant Q-waves in two contiguous leads or elevation of creatine kinase, MB fraction (CK-MB) or CK greater than three times the upper limit of normal constituted an MI. The EPIC trial required only one abnormal enzyme value, whereas the other two trials required two values. After hospital discharge, MI was defined as either new Q-waves or elevation of CK-MB or CK greater than twice the upper limit of normal. When available, CK-MB took precedence over CK.

Statistical analysis. Data from the three trials were pooled, and a Breslow-Day test was performed to ensure homogeneity of the outcome across trials. Kaplan-Meier survival estimates and hazard ratios with 95% confidence intervals (CIs) were calculated for the primary end point of death at one year. Secondary end points included MI and target vessel revascularization (TVR). Predetermined subgroups for analysis were diabetics classified as insulin-requiring, patients with insulin-resistance syndrome, and diabetics who underwent multivessel intervention. The log-rank test was used to compare event rates among treatment groups for all subgroups. A Cox proportional hazards survival model was used to calculate hazard ratios and 95% CIs for the subgroups after adjusting for baseline characteristics in a final model. An unadjusted alpha value of 0.05 was used for all analyses. All statistical calculations were performed using SAS Software, version 6.12 (SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. The baseline characteristics of the 5,072 nondiabetic and the 1,462 diabetic patients are listed in Table 1. Diabetic patients were more likely to be older, women, non-Caucasian, or have a history of hypertension, congestive heart failure (CHF), elevated BMI, or prior revascularization. Diabetics were less likely to have a prior or recent (within the last seven days) MI or to smoke currently.
There were no significant differences between the patients randomized to placebo or to abciximab.

**Mortality.** Diabetic patients had a higher one-year mortality than did nondiabetic patients, 3.3% versus 2.1%, \( p = 0.012 \) (Fig. 1). In the overall cohort, the 4,110 patients randomized to abciximab had lower mortality than did the 2,424 patients randomized to placebo, 2.0% versus 3.1%, \( p = 0.010 \) (Fig. 2). Abciximab treatment was associated with lower mortality in both the diabetic and the nondiabetic patients (Fig. 3). In nondiabetic patients, those who received placebo had a 48/1,850 (2.6%) mortality rate compared with a 61/3,222 (1.9%) rate with abciximab treatment, \( p = 0.099 \). In diabetic patients, placebo treatment resulted in a 26/574 (4.5%) mortality, versus 22/888 (2.5%) mortality with abciximab, \( p = 0.031 \). The event rate for diabetes treated with abciximab is comparable to that of placebo-treated nondiabetic patients. The reduction in mortality in diabetics was seen in both the 931 men (4.9% to 2.7%, \( p = 0.083 \)) and the 531 women (4.0% to 2.0%, \( p = 0.170 \)).

A mortality reduction in insulin-requiring diabetics with abciximab treatment was also noted. The one-year mortality rate for insulin-requiring diabetics treated with placebo was 16/197 (8.1%) versus 11/265 (4.2%) with abciximab treatment, \( p = 0.073 \). In the diabetic patients not receiving insulin therapy, the mortality rate was reduced from 10/377 (2.7%) to 11/623 (1.8%), \( p = 0.341 \).

Diabetic patients had a reduction in mortality regardless of whether they had balloon angioplasty or stent implantation; a Breslow-Day test showed no heterogeneity between devices, \( p = 0.694 \). Table 2 depicts the mortality rates seen in the patients who received stents and were randomized to abciximab. Among patients who underwent multivessel intervention, the mortality rate was 5/65 (7.7%) for diabetics receiving placebo versus 1/108 (0.9%) for diabetics receiving abciximab, \( p = 0.018 \).

**Death, MI or TVR.** Abciximab also reduced the combined end point of one-year death, MI, or TVR in diabetic patients, from 34.3% to 29.1%, \( p = 0.022 \). The rate of MI was reduced from 11.6% to 6.0%, \( p < 0.001 \). This was principally due to a reduction in the rate of non-Q-wave MI, which was reduced by abciximab therapy from 9.7% to 4.0%, \( p < 0.001 \); the rate of Q-wave MI was 2.2% in both the placebo and abciximab-treated diabetics. The rate of TVR was also slightly lower in the patients randomized to abciximab, 24.2% versus 25.2%, but this was not statistically significant (\( p = 0.674 \)). Of diabetic patients who were stented, there was less one-year TVR in those receiving abciximab compared with placebo, 16.7% versus 20.7%, though this did not reach statistical significance (\( p = 0.273 \)). Of diabetic patients who died by one year, 18.7% had a periprocedural CK elevation greater than three times the upper limit of normal, versus 8.2% of the diabetic patients who were alive (\( p = 0.010 \)).

**Patients with insulin resistance.** Patients who were classified as insulin resistant (i.e., diabetic, hypertensive and elevated BMI) were at particularly high risk of adverse events and derived a substantial benefit from abciximab. In these 720 patients, mortality was reduced by abciximab

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**Table 1.** Baseline Characteristics of Patients Classified as Diabetic or Nondiabetic

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic (( n = 5,072 ))</th>
<th>Diabetic (( n = 1,462 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59.4</td>
<td>60.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Women</td>
<td>24.0%</td>
<td>36.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>8.1%</td>
<td>15.0%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51.5%</td>
<td>70.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>4.8%</td>
<td>12.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>10.6%</td>
<td>15.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>20.2%</td>
<td>23.9%</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior MI</td>
<td>51.4%</td>
<td>48.8%</td>
<td>0.081</td>
</tr>
<tr>
<td>Recent MI</td>
<td>20.7%</td>
<td>15.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>28.2</td>
<td>30.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>37.0</td>
<td>25.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td>0.513</td>
</tr>
<tr>
<td>1-vessel</td>
<td>67.9</td>
<td>67.0</td>
<td></td>
</tr>
<tr>
<td>2-vessel</td>
<td>22.1</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>3-vessel</td>
<td>8.1</td>
<td>9.3</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index in kg/m²; CABG = coronary artery bypass grafting; CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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**Figure 1.** The Kaplan-Meier curves for one-year mortality in diabetics versus nondiabetics.

**Figure 2.** The Kaplan-Meier curves are shown for one-year mortality in patients randomized to either placebo or abciximab.
treatment from 5.1% to 2.3%, \(p = 0.044\), MI was reduced from 12.0% to 7.1%, \(p = 0.024\), and TVR was reduced from 32.7% to 25.7%, \(p = 0.048\). The combined end point of death, MI or TVR was reduced from 42.6% to 31.3%, \(p = 0.002\).

**Bleeding.** Slightly more bleeding occurred in diabetic patients treated with abciximab versus placebo; however, the differences in the rates of major bleeding (4.3% vs. 3.0%, \(p = 0.21\)) or of minor bleeding (6.9% vs. 6.3%, \(p = 0.66\)) were not statistically significant. The incidence of intracranial hemorrhage was very low in diabetic patients receiving placebo or abciximab (0.17% vs. 0%, \(p = 0.39\)).

**Consistency of benefit in each trial.** The benefit of abciximab in diabetics was seen in each of the three trials that were pooled; a Breslow-Day test showed no heterogeneity among the three trials that were combined for this analysis, \(p = 0.745\). In the EPIC trial the risk ratio for one-year mortality in diabetics treated with abciximab compared with placebo was 0.995 (95% CI 0.384–2.579); in EPILOG, the risk ratio was 0.430 (95% CI 0.170–1.089); and in EPISTENT, the risk ratio was 0.457 (95% CI 0.154–1.361). The pooled data showed a risk ratio of 0.541 (95% CI 0.306–0.954), \(p = 0.034\) (Fig. 4).

**Multivariable modeling.** Multivariable modeling for predictors of one-year mortality in the overall cohort revealed that abciximab use at the time of intervention was protective, with a hazard ratio of 0.642, \(p = 0.010\) (Table 3). The other predictors of mortality were a history of insulin-requiring diabetes, hypertension, CHF, age greater than or equal to 65 years, or a Type B2/C lesion. Stenting appeared to confer a protective effect. Other factors that were entered into the model but were not significant included gender, race, BMI, smoking status, multivessel disease, and history of MI. Restricting the analysis to diabetic patients, those categorized as insulin-requiring had a hazard ratio for mortality of 2.22 (95% CI 1.214–4.058), \(p = 0.010\), after adjusting for the same significant predictors listed above.

**DISCUSSION**

Diabetic patients have worse outcomes after PCI than do nondiabetic patients. Abciximab has been shown to improve outcomes after PCI in a broad range of patients (34). In addition to its beneficial effects on reducing periprocedural MI and the need for urgent revascularization, abciximab has more recently been shown to decrease mortality after stenting (37). The purpose of this investigation was to determine whether there is a mortality benefit of abciximab use in diabetic patients, given their high-risk profile. We found a striking 44% reduction in one-year mortality among diabetic patients who were randomized to treatment with abciximab at the time of PCI. Treatment with abciximab essentially equalized outcomes of diabetic patients to those of placebo-treated nondiabetics. The benefit of abciximab in diabetic patients was evident in the combined end point of death, MI or TVR as well.

The patients classified as insulin-requiring had an even higher mortality than did the non-insulin-requiring diabetic patients, as previous studies have also reported (38). In our analysis abciximab appeared to have a strong mortality benefit in those patients receiving insulin. It is impossible to determine from this study whether insulin treatment merely served as a marker for more severe diabetes or whether insulin therapy itself had a deleterious effect. Diabetic patients who were also hypertensive and obese (elevated BMI) had particularly high rates of adverse outcomes. Abciximab reduced the one-year risk of death, MI or TVR by over 25% in this high-risk cohort.

Whether stenting per se improves outcomes in diabetics has been debated. While it appears that stenting may reduce the restenosis rate in diabetics, it does not impact on their higher risk of MI or death (39,40). In our study, the combination of abciximab and stent placement produced particularly favorable results in diabetics. Thus, the combi-

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**Table 2.** One-Year Mortality Rates in Patients Undergoing Either Balloon Angioplasty or Stent Placement Who Were Randomized to Placebo or Abciximab

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 2,252)</th>
<th>Abciximab (n = 3,844)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiabetic/Balloon</td>
<td>30/995 (3.0%)</td>
<td>44/2082 (2.1%)</td>
<td>0.127</td>
</tr>
<tr>
<td>Diabetic/Balloon</td>
<td>17/343 (5.0%)</td>
<td>18/614 (2.9%)</td>
<td>0.110</td>
</tr>
<tr>
<td>Nondiabetic/Stent</td>
<td>13/717 (1.8%)</td>
<td>11/918 (1.2%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Diabetic/Stent</td>
<td>9/197 (4.6%)</td>
<td>3/230 (1.3%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>
nation of abciximab with stenting may be the optimal percutaneous revascularization strategy, not only for reducing TVR (32) but also for improving survival.

Previous studies have suggested that diabetic patients who undergo multivessel angioplasty have increased mortality compared to those who undergo bypass surgery (41–45). These studies have prompted consideration of abandoning multivessel intervention in the diabetic population (46). Our analysis showed a reduction in mortality among diabetics randomized to abciximab who had multivessel intervention performed. Given the remarkable benefit of abciximab in reducing mortality in diabetics, the issue of multivessel PCI with concomitant GP IIb/IIIa inhibition (and stents) versus coronary artery bypass surgery with arterial grafts should be reexplored (47–49).

Potential mechanism of benefit. The mechanism of abciximab's marked benefit in reducing mortality in diabetics is unclear. A larger proportion of the patients who died had a significant periprocedural elevation in cardiac enzyme levels than did patients who did not die. Abciximab has a powerful ability to reduce periprocedural MI, and part of its effect on mortality may be mediated through this effect. However, the majority of patients who died did not have a periprocedural MI. Thus, other protective mechanisms of abciximab must be operative.

Prevention of distal embolization and microvascular injury may be of long-term importance. The microvasculature of diabetics is often diffusely diseased and may be poorly suited to handle the thromboembolic burden created by PCI. Perhaps instrumentation of the artery and microscopic injury contribute to new lesion development (50). Periprocedural abciximab administration may attenuate the response of the endothelium to such injury by means of its binding to receptors other than the GP IIb/IIIa receptor (51). Abciximab's modulation of cell adhesion molecules may be of particular importance in the diabetic (52,53). Abciximab's possible benefit in reducing neointimal growth, as documented by angiography in stented patients, is another intriguing mechanism of benefit (31,32,54). The success of the one-time administration of an antiplatelet agent at the time of intervention raises the possibility of even greater improvement in outcomes with long-term oral antiplatelet therapy (55).

Study limitations. There were certain limitations to this study. This was not a dedicated, randomized clinical trial of diabetic patients, but rather a retrospective analysis of the cohort of diabetics from the three trials studied. However, the assignment to abciximab was randomized, and the placebo and drug groups appeared well balanced. Detailed information about diabetic status was not collected. There was no information about fasting glucose values or levels of glycosylated hemoglobin. Thus, the severity and extent of control of diabetes was not known, nor was the duration.

Furthermore, classification of diabetics as insulin-requiring or non-insulin-requiring was based on whether patients were taking insulin. Information about specific medications used to treat diabetes was incomplete; sulfonylureas may themselves increase mortality in diabetics in certain settings (56–58). Differentiation between diabetics taking oral medication or diabetics treated with dietary modification alone was not possible. Data on hyperlipidemia were also incomplete. In addition, in the patients who died, the actual cause of death was not recorded.

Conclusions. Diabetic patients, and insulin-requiring diabetics in particular, derived a significant one-year mortality benefit from prophylactic abciximab administration at the time of either balloon angioplasty or stent deployment. Further investigation is necessary to delineate the precise mechanism responsible for this reduction in mortality. Abciximab use should be strongly considered at the time of intervention in diabetic patients, especially those who are being treated with insulin or are also hypertensive and obese.

Finally, based on our findings, a randomized trial of PCI with concomitant GP IIb/IIIa blockade versus coronary artery bypass surgery may be warranted to establish the superior mode of revascularization in diabetics with multivessel coronary disease.
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