Optimizing the Percutaneous Interventional Outcomes for Patients With Diabetes Mellitus

Results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) Diabetic Substudy

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Background—Stenting likely decreases the need for target-vessel revascularization procedures in diabetic patients compared with balloon angioplasty. However, the efficacy of stenting with platelet glycoprotein IIb/IIIa blockade has not yet been assessed in diabetics.

Methods and Results—We analyzed the outcomes of 491 diabetic patients within the multicenter Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT). Diabetic patients were a prospectively defined subset: 173 were randomized to stent-placebo, 162 to stent-abciximab, and 156 to balloon angioplasty–abciximab. The main end point for this analysis was combined 6-month death, myocardial infarction (MI), or target-vessel revascularization (TVR). The composite end point occurred in 25.2% of stent-placebo, 23.4% of balloon-abciximab, and 13.0% of stent-abciximab patients ($P=0.005$). Abciximab therapy, irrespective of revascularization strategy (stent or balloon angioplasty), resulted in a significant reduction in the 6-month death or MI rate: 12.7% for stent-placebo, 7.8% for balloon angioplasty–abciximab, and 6.2% for the stent-abciximab group ($P=0.029$). The 6-month TVR rate was 16.6% for stent-placebo, 18.4% for balloon-abciximab, and 8.1% for stent-abciximab ($P=0.021$). Compared with stent-placebo, stent-abciximab therapy was associated with a significant increase in angiographic net gain (0.88 versus 0.55 mm; $P=0.011$) and a decrease in the late loss index (0.40 versus 0.60 mm; $P=0.061$). The 1-year mortality rate for diabetics was 4.1% for stent-placebo and 1.2% for stent-abciximab patients ($P=0.11$).

Conclusions—The combination of stenting and abciximab therapy among diabetics resulted in a significant reduction in 6-month rates of death, MI, and TVR compared with stent-placebo or balloon-abciximab therapy. **(*Circulation*. 1999;100:2477-2484.)**

Key Words: stents ■ diabetes mellitus ■ restenosis ■ platelet aggregation inhibitors

Numerous clinical studies[1–3] have demonstrated diabetes mellitus, whether insulin dependent or non-insulin dependent, to be an important determinant of angiographic restenosis, the need for additional revascularization procedures, and late mortality after conventional balloon angioplasty. Compared with balloon angioplasty, stenting has been shown in recent years to potentially improve intermediate outcome for diabetic patients.[4] Unfortunately, diabetics continue to have increased rates of clinical events and restenosis after percutaneous coronary intervention (PCI).[5–7] Concurrently, abciximab (ReoPro; Centocor, Malvern, Pa) has been shown to improve the safety profile for both balloon angioplasty and stenting[8–12] in a variety of clinical settings. However, whether there is an additional benefit of stenting plus abciximab compared with stenting alone or PTCA-abciximab in diabetic patients is unknown. Therefore, we performed an analysis of all diabetic patients, a prospectively defined subset, within the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT).

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Methods

The details of patient selection, inclusion criteria, methods, and adjunctive pharmacotherapy have been reported previously.[11] Briefly, patients enrolled were eligible to undergo stenting or balloon

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angioplasty and had an epicardial coronary stenosis ≥60% during the time period of July 1996 through September 1997. Patients were randomized to 1 of 3 groups. Abciximab was administered as a 0.25 mg/kg bolus 10 to 60 minutes before balloon inflation or device delivery, followed by a 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (maximum of 10 μg/min) infusion for 12 hours. Patients in the abciximab-treated group received a low-dose weight-adjusted heparin regimen, whereas patients in the placebo group received a standard-dose weight-adjusted heparin regimen.[9] Investigators were blinded to the heparin-dosing regimen in the stent arms.

There were 491 diabetics within EPISTENT. Diabetic patients were identified by patient-reported history, and their diabetes was managed with insulin, oral hypoglycemic agents, diet alone, or any combination thereof. Myocardial infarction (MI) was defined as new pathological Q waves or creatinine kinase (CK) or MB isoenzyme levels >3 times the upper limit of normal during index hospital admission and 2 times the upper limit of normal after index admission. A large MI was defined as CK (or MB isoenzyme) levels >5 times the upper limit of normal, new pathological Q-waves on ECG, or posthospitalization non–Q-wave MI. Determination of all MIs was by systematic review of the 12-lead ECGs and CK data by the clinical events committee. Recent MI was defined as an MI within 7 days of the index intervention. A recent smoker was defined as a current smoker or one who quit smoking within 1 year.

At participating sites, the first 899 consecutive patients in EPISTENT were enrolled in the angiographic substudy and gave consent for repeat angiography after randomization. There were 183 diabetic patients enrolled in the angiographic substudy. Angiographic core laboratory personnel who were blinded to study assignment performed all angiographic analyses using quantitative computerized analysis.

End Points

The main end point for this substudy was the composite end point of all-cause mortality, nonfatal MI, or target-vessel revascularization (TVR) at 6-month follow-up. Other end points included death and large MI at 6 months and death at 1 year. Clinical event committee members who were blinded to study group assignment determined the end points, including determination of MI.

Statistical Analysis

Baseline characteristics were summarized by the use of frequencies and percentages (of nonmissing data) for categorical factors and means and SDs for continuous factors. For the categorical variables, χ^2 or exact tests were used to compare treatment groups, and ANOVA techniques or Kruskal-Wallis tests were used for continuous data. Kaplan-Meier methods were used to estimate event rates for each treatment group. Comparisons of event rates between each of the abciximab arms and the placebo-stent arm were performed with log-rank tests. Stepwise regression methods were used to determine the factors independently associated ($P<0.05$) with the 6-month main composite end point and TVR. Risk ratios, 95% CIs of the risk ratios, and Wald χ^2 probability values from the multivariate Cox proportional hazard models are reported.

For the angiographic substudy, an ANOVA was used to evaluate the differences between each abciximab arm and the placebo-stent arm. For these models, the unit of analyses was the average of 2 views of each lesion (multiple lesions per patient were possible), and both the patient and lesion within patient were considered as random effects. SAS PROC MIXED software was used to model within-patient covariance.

We compared TVR rates for patients with clinical markers for insulin resistance syndrome (obesity, which was prospectively defined as body mass index >27 kg/m^2 for females and >28 kg/m^2 for males; history of hypertension; and diabetes) with a non–insulin-resistant cohort: nonobese, nondiabetic, and nonhypertensive individuals.

Results

Baseline characteristics of the diabetic and nondiabetic patients are listed in Table 1. The baseline characteristics of the 491 diabetics randomized to the 3 treatment arms are shown in Table 2. Table 3 demonstrates the baseline angiographic characteristics of the study groups. There were fewer vein graft interventions in the stent-abciximab group.

TABLE 1. Baseline Clinical Characteristics for Diabetics and Nondiabetics

	Diabetic (n=491)	Nondiabetic (n=1908)	P*
Age, y	60.4±10	59.2±11	0.035
Female	143 (29)	455 (24)	0.016
BMI	31±5.6	29±4.8	<0.001
Hypertension	335 (69)	924 (49)	<0.001
Heart failure	48 (10)	65 (3)	<0.001
PVD	34 (7)	92 (5)	0.064
Recent smoker	142 (30)	736 (39)	<0.001
Prior MI	233 (48)	941 (49)	0.5
Recent MI	76 (16)	317 (17)	0.5
Prior PCI	83 (17)	281 (15)	0.2
Prior CABG	49 (10)	168 (9)	0.4

BMI indicates body mass index; PVD, peripheral vascular disease.
Data listed as mean±SD or number (percent of group).
*Three-way *P* value.

There was 98.7% follow-up for the diabetic cohort at 6 months. The 6-month event rates for the diabetic and nondiabetic patients are shown in Table 4. For the diabetic cohort, there was a significant reduction in the 6-month combined event rate of death, MI, or TVR for the stent-abciximab group compared with both the stent-placebo and PTCA-abciximab groups (Table 4 and Figure 1A). The reduction in the combined event rate for stent and abciximab-treated diabetic patients was chiefly determined by 2 factors. First, abciximab administration, irrespective of revascularization assignment, resulted in a significant reduction in the 6-month rate of death or MI (Figure 1B). Second, in the diabetic cohort, there was a >50% reduction in the 6-month TVR rate for the stent-abciximab group compared with the stent-placebo and PTCA-abciximab groups (Figure 1C). Diabetics in the stent-abciximab group had a similar 6-month TVR rate compared with nondiabetic patients treated with stent-abciximab (Figure 1D). Stenting without the use of abciximab resulted in a significant increase in the 6-month TVR rate for diabetics compared with nondiabetics (16.6% versus 9.0%; $P=0.005$). This stent-abciximab TVR interaction was not seen in the nondiabetic cohort. As seen in Table 4, stenting alone in nondiabetics resulted in a significant reduction in the 6-month TVR rate compared with the PTCA-abciximab group.

The hazard ratio point estimates and 95% confidence limits of the 6-month events for the diabetic patients in the stent-abciximab and stent-placebo groups are shown in Figure 2. There was both an absolute reduction of events and a consistency of the directionality and magnitude of benefit for all end points analyzed for the stent-abciximab group compared with the stent-placebo group for the diabetic cohort.

There was also a trend for improved 1-year survival for diabetics who were randomized to the stent-abciximab arm. The 1-year mortality rate was 4.1% for the stent-placebo

TABLE 2. Baseline Clinical Characteristics for Diabetic Patients

	Stent-Placebo (n=173)	Stent-Abciximab (n=162)	PTCA-Abciximab (n=156)	P*
Age, y	60.9±10	60.9±10	59.3±11	0.2
Male	120 (69)	117 (72)	111 (71)	0.8
BMI	30.8±6	31.3±6	30.8±5	0.7
Hypertension	123 (71)	100 (63)	112 (72)	0.1
Heart failure	14 (8)	18 (11)	16 (10)	0.6
PVD	8 (5)	11 (7)	15 (10)	0.2
Prior PCI	24 (14)	25 (15)	34 (22)	0.1
Prior CABG	26 (15)	9 (6)	14 (9)	0.01
Recent smoker	55 (33)	43 (27)	44 (29)	0.5
Prior MI	97 (56)	63 (39)	73 (47)	0.007
Recent MI	31 (18)	22 (14)	23 (15)	0.5
Diabetes treatments				0.002
Insulin	39 (23)	24 (16)	43 (30)	
Oral hypoglycemic	96 (57)	82 (55)	76 (52)	
Both	12 (7)	4 (3)	3 (2)	

BMI indicates body mass index; PVD, peripheral vascular disease.
Data listed as mean±SD or number (percent of group).
*Three-way *P* value.

group compared with 1.2% for the stent-abciximab group ($P=0.11$). The PTCA-abciximab group had an intermediate 1-year mortality rate of 2.6%.

Given the imbalance in some of the baseline clinical and angiographic characteristics among the study groups, a multivariate model was developed for the 6-month combined end point to adjust for these observed differences. The benefit of stenting with abciximab in diabetics remained significant after multivariate adjustment (hazard ratio [HR] 0.48, 95% CI 0.28 to 0.83, $P=0.008$). Other significant predictors of the combined end point included hypertension (HR 1.87, 95% CI 1.1 to 3.1, $P=0.015$), recent history of smoking (HR 0.48, 95% CI 0.28 to 0.81, $P=0.006$), prior PCI (HR 2.0, 95% CI 1.3 to 3.2, $P=0.003$), and type B2 or C lesions (HR 1.7, 95% CI 1.1 to 2.7, $P=0.029$). To further characterize the benefit of stenting with abciximab in diabetic patients, we excluded diabetics who were treated with diet alone. There were 110 (67.9% of group) treated diabetics in the stent-abciximab group and 140 (81% of group) treated diabetics in the stent-placebo group. In this subgroup of treated diabetics, not only was there a significant reduction in the 6-month combined event rate for the stent-abciximab group compared with the stent-placebo group (14.6% versus 26.1%; $P=0.026$), but in addition, the degree of absolute benefit was similar to that

TABLE 3. Baseline Angiographic Characteristics of Diabetic Patients

	Stent-Placebo (n=173)	Stent-Abciximab (n=162)	PTCA-Abciximab (n=156)	P*
Number of treated vessels				0.3
None	11 (6.4)	4 (2.5)	5 (3.2)	
Single	148 (85.5)	142 (87.7)	131 (84)	
Double	13 (7.5)	15 (9.5)	20 (12.8)	
Triple	1 (0.6)	1 (0.6)	0 (0.0)	
Pre-PCI % stenosis	88±9	88±8	87±9	0.8
Pre-PCI TIMI III	134 (82)	134 (85)	121 (83)	0.7
B2 or C	119 (71)	108 (68)	89 (60)	0.1
Lesion length, mm				0.2
<10	70 (41)	72 (45)	73 (48)	
10–20	89 (52)	79 (45)	63 (42)	
>20	12 (7)	8 (5)	15 (10)	
Ostial location	15 (9)	10 (6)	8 (5)	0.4
Native coronary intervention	158 (91)	157 (98)	150 (98)	0.004

*Three-way *P* value. B2 or C indicates American College of Cardiology/American Heart Association lesion classification system.

TABLE 4. 6-Month Event Rates for Study Groups

	Stent-Placebo (n=809)	Stent-Abciximab (n=794)	P*	PTCA-Abciximab (n=796)	P†
Death, MI, or TVR					
Diabetics	43 (25.2)	21 (13.0)	0.005	36 (23.4)	0.6
Nondiabetics	104 (16.5)	81 (13.0)	0.062	126 (19.9)	0.17
Death or MI					
Diabetics	22 (12.7)	10 (6.2)	0.041	12 (7.8)	0.13
Nondiabetics	70 (11.0)	34 (5.4)	<0.001	50 (7.8)	0.049
Death					
Diabetics	3 (1.7)	1 (0.6)	0.35	2 (1.3)	0.74
Nondiabetics	7 (1.1)	3 (0.5)	0.21	12 (1.9)	0.26
MI					
Diabetics	19 (11.0)	10 (6.2)	0.11	10 (6.5)	0.14
Nondiabetics	64 (10.1)	31 (4.9)	<0.001	42 (6.6)	0.024
TVR					
Diabetics	28 (16.6)	13 (8.1)	0.021	28 (18.4)	0.7
Nondiabetics	56 (9.0)	55 (8.8)	0.95	92 (14.6)	0.002

*Stent-placebo vs stent-abciximab; †stent-placebo vs PTCA-abciximab.

seen in the entire diabetic cohort. There was also a similar reduction in the 6-month TVR rate for the stent-abciximab group compared with the stent-placebo group for the treated-diabetic cohort (9.2% versus 18.2%; $P=0.047$). The 1-year all-cause mortality rate for treated diabetics was 4.8% in the stent-placebo group compared with 0.9% in the stent-abciximab group ($P=0.08$).

There were 165 of 183 patients eligible for angiographic follow-up. Eighteen patients were ineligible for the following reasons: no intervention was performed (n=8), residual stenosis was >50% (n=5), patient underwent revascularization within 7 days of index intervention (n=2), patient died (n=1), or no repeat angiogram was performed before revascularization after 7 days of index intervention (n=2). There

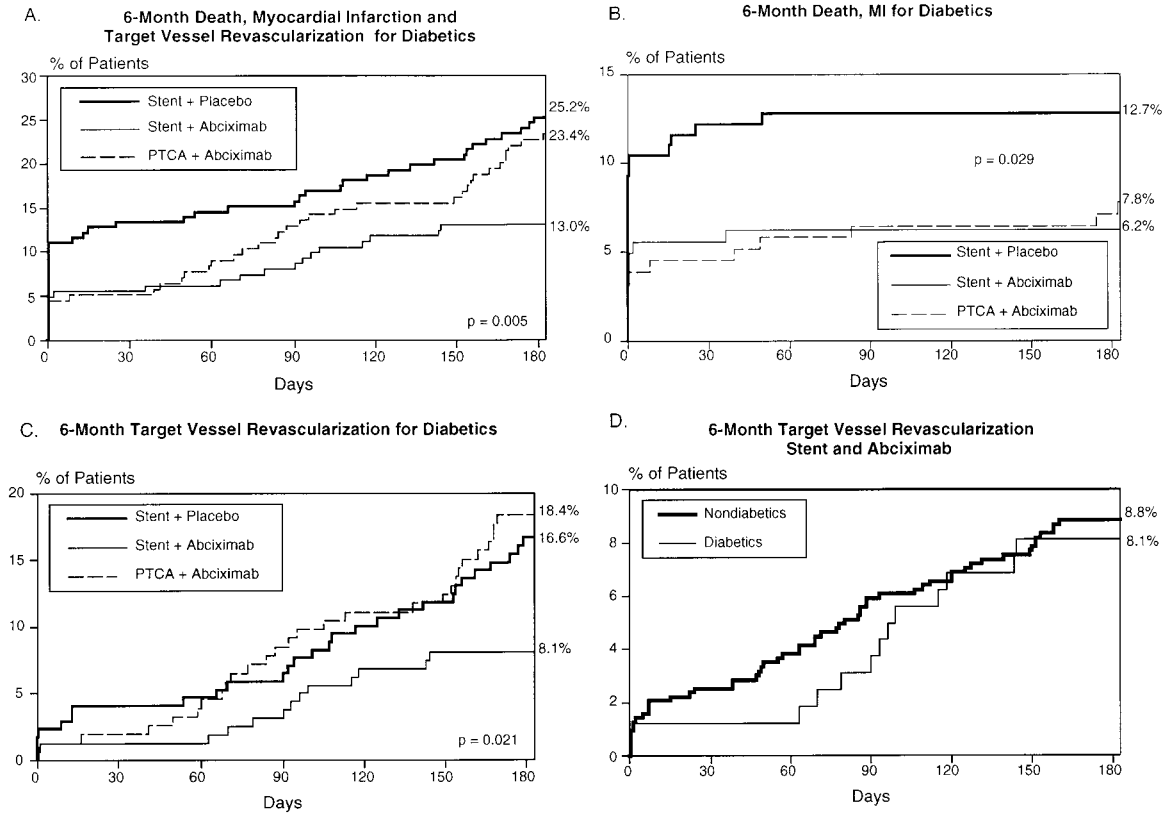

Figure 1. A-D, Kaplan-Meier estimates for depicted end points and study groups.

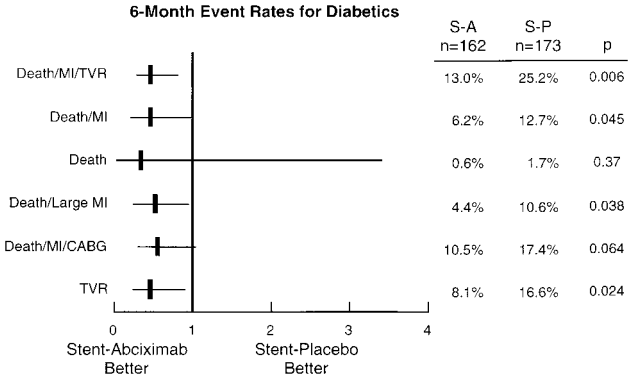

Figure 2. Absolute percentage of events, 95% confidence limits, and point estimates of listed end points for diabetics randomized to either stenting-abciximab (S-A) or stenting-placebo (S-P).

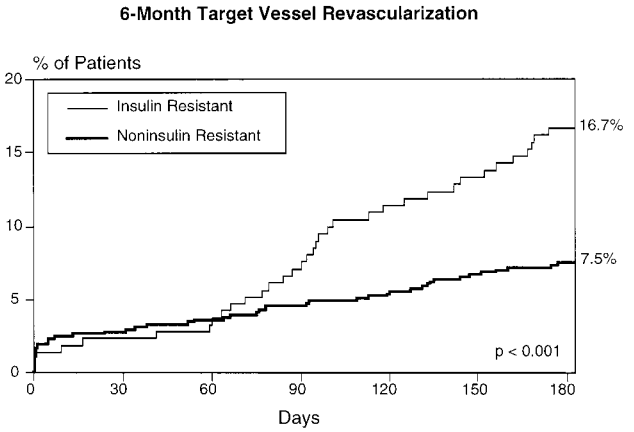

Figure 3. Kaplan-Meier estimates for 6-month TVR. Insulin resistance indicates patients with hypertension, obesity, and diabetes; noninsulin resistance, patients without hypertension, obesity, and diabetes.

were 128 patients (77.5% of the eligible group) who underwent angiographic follow-up. There were 27 eligible patients who did not undergo follow-up angiography. Six patients were lost to follow-up, 18 refused follow-up, angiography was contraindicated in 2, and 1 patient did not undergo angiography for administrative reasons. Preprocedure minimal lumen diameter was lower in patients in the groups treated with stent-abciximab or PTCA-abciximab than in the stent-placebo group (Table 5). Acute gain and late loss were greater for the stent-treated patients. At 6 months, net gain was similar for the diabetic patients treated with PTCA-abciximab or stent-placebo. Stenting-abciximab therapy was associated with a significant 60% increase in net gain compared with the stent-placebo group (0.88 versus 0.55 mm; $P=0.011$). This translated into a 33% decrease in the late loss index for the stent-abciximab group (0.40 versus 0.60; $P=0.061$) compared with the stent-placebo group. The results of the angiographic substudy were similar if analyzed on a per-patient basis (multiple treated lesions per patient were possible). This analysis resulted in 64 lesions that underwent intervention in the stent-placebo group, 64 lesions in the stent-abciximab group, and 47 lesions in the PTCA-abciximab group. In this analysis, stent-abciximab resulted in a significant increase in net gain (0.85 versus 0.51; $P=0.003$), which translated into a decrease in late loss index (0.38 versus 0.64; $P=0.039$) compared with the stent-placebo group. The 6-month binary restenosis rate (defined as >70% luminal narrowing) was 14.3% for the stent-placebo group and 7.8% for the stent-abciximab group ($P=0.25$). The restenosis rate for the PTCA-abciximab group was 19.6%.

The 6-month TVR rates for those patients with and without clinical markers of insulin resistance in the entire EPISTENT cohort are shown in Figure 3. There were 215 patients with obesity, hypertension, and diabetes and 615 patients who were neither diabetic nor obese and had no history of hypertension. The 6-month TVR rate for patients with clinical markers of insulin resistance was 16.7% compared with 7.5% for patients without clinical markers of insulin resistance ($P<0.001$). To identify other potential clinical predictors of 6-month TVR, a multivariate Cox proportional hazards model considering all collected baseline clinical characteristics was developed for the end point of TVR based on the entire EPISTENT cohort. The significant clinical predictors of 6-month TVR are shown in Table 6. We were unable to identify other clinical predictors of restenosis in this cohort. There appears to be an important diabetes-stent/abciximab interaction with regard to 6-month TVR. Clinical markers of insulin resistance remained significant predictors of TVR after multivariate analysis.

Discussion

Stenting plus abciximab resulted not only in an improved safety profile for stenting in diabetics, as measured by a

TABLE 5. Results of the 6-Month Angiographic Substudy for Diabetics

	Stent-Placebo (n=46)	Stent-Abciximab (n=46)	P*	PTCA-Abciximab (n=57)	P†
Preprocedure MLD, mm	0.91±0.44	0.78±0.36	0.069	0.86±0.28	0.56
Postprocedure MLD, mm	2.37±0.45	2.35±0.44	0.671	1.81±0.41	<0.001
Follow-up MLD, mm	1.48±0.70	1.66±0.59	0.14	1.29±0.49	0.11
Acute gain, mm	1.45±0.58	1.58±0.54	0.24	0.96±0.49	<0.001
Late loss, mm	0.90±0.67	0.69±0.63	0.098	0.50±0.56	0.003
Net gain, mm	0.55±0.69	0.88±0.62	0.011	0.43±0.52	0.34
Loss index	0.60±0.42	0.40±0.41	0.061	0.45±0.76	0.21

Data listed as mean±SD. MLD indicates minimal luminal diameter.
*Stent-placebo vs stent-abciximab; †stent-placebo vs PTCA-abciximab.

TABLE 6. Multivariate Cox Proportional Hazards Model for 6-Month TVR for the Entire EPISTENT Cohort*

	Hazard Ratio	95% Confidence Limits	P
PTCA-abciximab	1.71	1.23, 2.38	0.002
Hypertension	1.68	1.30, 2.17	<0.001
Body mass index	1.02	1.0, 1.05	0.046
Diabetes mellitus	1.62	1.02, 2.56	0.039
Stent/abciximab-diabetes interaction	0.49	0.23, 1.04	0.063

*Stent-abciximab and PTCA/abciximab-diabetes interaction terms were also used in this analysis. Neither was significant.

reduction in the 6-month rate of death or MI, but also in a significant reduction in the need for repeat percutaneous or surgical revascularization procedures. In this subset of patients, a trend for improved survival for the diabetic stent-abciximab–treated group emerged at 1-year follow-up. We also identified an important clinical predictor of restenosis among diabetic patients: the triad of obesity, hypertension, and diabetes mellitus. There was a >2-fold increase in the 6-month TVR rate for patients with these clinical hallmarks of insulin resistance, which remained significant after multivariate analysis.

No subgroup of patients has generated more controversy in recent years than diabetics who require coronary revascularization. Interest seems to have been piqued when the National Heart, Lung, and Blood Institute issued a clinical alert to physicians stating that coronary artery bypass surgery should be considered the preferred revascularization procedure in diabetic patients with multivessel disease who require an initial coronary revascularization procedure.[13] These comments were predicated on the BARI (Bypass Angioplasty Revascularization Investigation) trial,[1] which demonstrated an improved 5-year survival rate for treated diabetics who underwent bypass surgery compared with balloon angioplasty (80.6% versus 65.5%; $P=0.003$). This trial was published in the background of multiple observational studies that demonstrated prohibitive restenosis and adverse clinical event rates in diabetics compared with nondiabetics after conventional balloon angioplasty. The poor historical outcomes of diabetics after balloon angioplasty, coupled with the results of the BARI trial and recent observational studies[14,15] that also suggested an improved outcome for diabetics after surgical revascularization, have prompted many to reconsider the role of PTCA for diabetic patients.

Whether stenting without the use of adjunctive glycoprotein (GP) IIb/IIIa blockade provides additional benefit compared with balloon angioplasty in diabetic patients remains an unresolved issue.[4,5] An initial observational study[5] suggested that compared with nondiabetics, diabetics continued to have excessive rates of restenosis after stenting (55% versus 20%; $P=0.001$). The increased restenosis rate after stenting in diabetic patients resulted from a significant increase in late loss for diabetics compared with nondiabetics (1.66 versus 1.23 mm; $P=0.04$). This initial study suggested that stenting did not substantially improve restenosis rates in diabetic patients. However, Van Belle and colleagues[4] demonstrated a more favorable outcome for diabetic patients after stenting. In that study, balloon angioplasty was associated with a significant increase in restenosis rates for diabetics compared with nondiabetics (63% versus 36%; $P=0.0002$). Restenosis rates for stenting were similar for diabetics and nondiabetics (25% versus 27%, respectively). Diabetics were not randomized to either stenting or balloon angioplasty; thus, definitive conclusions regarding the improved efficacy of stenting in diabetics are difficult to reach.

Platelets may be a particularly key modulator of thrombosis in diabetics, because platelets of diabetic patients are known to be larger, to have a greater number of GP IIb/IIIa receptors,[16] and to aggregate more readily in vitro to known agonists compared with platelets of nondiabetics.[17] Diabetic platelets seem to have an increased population of activated circulating platelets,[18] which express activation-dependent adhesion molecules such as activated $\alpha_2\beta_3$ (GP IIb/IIIa), lysosomal GP53, thrombospondin, and P-selectin (CD62).[19] Among other interactions, these adhesion molecules can also mediate platelet-leukocyte interactions, potentially resulting in an enhanced inflammatory response that leads to further injury and the tendency for thrombosis.[20] Using a unique device, the cone and plate(let) analyzer, Knobler et al[21] measured shear-induced whole-blood platelet adhesion and aggregation on extracellular matrices of diabetics and nondiabetics. This model maintains the presence of other blood elements, shear force, and solid-phase subendothelial components. The study demonstrated increased platelet adhesion and aggregation in diabetic patients, which loosely correlated with the degree of dyslipidemia.

Although antiplatelet therapy has not consistently been shown to prevent restenosis in previous studies, inhibition of platelet aggregation via GP IIb/IIIa receptor inhibitors seems to be important in the prevention of restenosis in diabetics after stenting. Restenosis after balloon angioplasty occurs as a function of acute vessel recoil, maladaptive arterial remodeling, or neointimal formation. Because stenting effectively prevents elastic recoil and adverse remodeling, restenosis after stenting is directly proportional to the degree of neointimal proliferation. Diabetics seem to have an increased propensity for neointimal proliferation after both stenting and balloon angioplasty.[22] The mechanism for the improved restenosis rates observed in the stent-abciximab–treated diabetics in the present study is unknown but may be related to decreased mural thrombus with abciximab administration. Arterial injury leads to endothelial denudation and platelet adhesion, activation, and aggregation, which ultimately leads to mural thrombus formation. Mural thrombus may be an important factor in developing restenosis[23,24] and likely serves as a lattice for the infiltration of smooth muscle cells, resulting in neointima formation. It is also solely dependent on fibrinogen forming cross-bridges with platelets via the GP IIb/IIIa receptor. Prevention of mural thrombus formation with abciximab is a plausible mechanism for the prevention of neointimal proliferation in diabetics after stenting. Abciximab not only binds to the GP IIb/IIIa receptor on platelets but also has a high affinity for the $\alpha_v\beta_3$ (vitronectin) receptor.[25] The $\alpha_v\beta_3$ receptor is highly expressed on endothelial and smooth muscle cells. This receptor has been shown to be important for neointimal proliferation and smooth muscle cell

migration. Whether this mechanism is borne out as a key inhibitor of neointimal proliferation in diabetics after stenting remains to be determined but is of great interest.

Abciximab has not been consistently shown to reduce angiographic restenosis in prior balloon angioplasty studies. Although the EPIC (Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications) trial demonstrated a 26% reduction in the TVR rate, subsequent trials were unable to replicate this finding. Abciximab does not appear to be effective in reducing restenosis rates for diabetics after balloon angioplasty. The EPILOG (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIIa receptor blockade) trial demonstrated a reduction in the rate of 1-year death and MI for diabetic patients, but there was no overall reduction in the TVR rate for abciximab-treated diabetics. EPILOG was primarily a balloon angioplasty trial, and only 12% of patients within this trial received a stent. The ERASER (Evaluation of ReoPro And Stenting to Eliminate Restenosis) trial was designed to determine whether abciximab resulted in decreased neointimal proliferation after stenting.[26] The primary end point was percent volumetric obstruction by intravascular ultrasound assessment. There was no overall difference in the primary end point for those patients randomized to placebo or abciximab. Although there were only 19 diabetics in the ERASER study, there was less percent obstruction in the diabetic abciximab-treated group. There was a 35.2% obstruction in the diabetic placebo group, 27.2% for the diabetic group with 12-hour infusion of abciximab, and 30.6% for the diabetic group with 24-hour infusion of abciximab.

Insulin Resistance

Insulin resistance is a state in which peripheral tissues have a decreased sensitivity to insulin, which leads to increased circulating insulin levels to maintain euglycemia. This insulin resistance syndrome precedes the onset of overt diabetes by many years and is associated with hypertension, obesity, dyslipidemia, and impaired fibrinolysis. Although insulin resistance has been correlated with the risk of macrovascular disease, this link has not been demonstrated clearly, and a recent meta-analysis by Ruige and colleagues[27] demonstrated only a weakly positive association of increased insulin level and risk of cardiovascular disease. In the present substudy, the clinical hallmarks of insulin resistance were important predictors of 6-month TVR rates, and the triad of hypertension, obesity, and diabetes remained significant after multivariate adjustment. Although these initial data are intriguing, the relationship between insulin resistance and restenosis will need to be corroborated in a larger cohort.

Study Limitations

Although patients with diabetes constituted a prespecified subset, treatments were assigned randomly, and 491 patients with diabetes mellitus were included in the EPISTENT study, there were differences in the baseline characteristics of the 3 treatment arms. However, the treatment benefit of stent-abciximab persisted after multivariate analysis. There was also a significant reduction of events in treated diabetics, and there was an apparent stent-abciximab interaction with regard to reduction in the 6-month TVR rates. In addition, only limited diabetes-related covariates were collected. Thus, we are unable to comment on the importance of glucose control or the association between events and the presence of diabetic nephropathy or to make specific conclusions regarding the impact of circulating insulin levels on restenosis. This subgroup of patients with diabetes mellitus is a select group who were eligible for stenting and who predominantly had single-vessel disease. It has been shown in numerous studies that diabetic patients have an increasing risk for events in long-term follow-up. Thus, follow-up of this cohort for an extended period of time and the obtainment of additional data on diabetics with multivessel disease will be important to further elucidate the benefit of abciximab administration to diabetic patients.

Conclusions

These data provide compelling evidence that the treatment strategy of stenting plus abciximab both improves the safety profile for stenting and decreases the need for future revascularization procedures in diabetic patients.

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Optimizing the Percutaneous Interventional Outcomes for Patients With Diabetes Mellitus: Results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) Diabetic Substudy

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