Randomized Clinical Trial of Abciximab in Diabetic Patients Undergoing Elective Percutaneous Coronary Interventions After Treatment With a High Loading Dose of Clopidogrel

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Background—Diabetic patients are at increased risk of adverse outcomes after percutaneous coronary interventions. Although subset analyses suggest particular benefit from the administration of abciximab in diabetic patients, no dedicated large randomized trials have been performed in diabetic patients undergoing percutaneous coronary intervention, and certainly not after pretreatment with a high loading dose of clopidogrel.

Methods and Results—This study (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics [ISAR-SWEET] Study) enrolled 701 diabetic patients with coronary artery disease who underwent an elective percutaneous coronary intervention after pretreatment with a 600-mg dose of clopidogrel >2 hours before the procedure: 351 patients were randomly assigned to abciximab and 350 patients to placebo. The primary end point of the trial was the composite incidence of death and myocardial infarction at 1 year. The frequency of angiographic restenosis (diameter stenosis ≥50%) was the secondary end point. The incidence of death or myocardial infarction was 8.3% in the abciximab group and 8.6% in the placebo group (P=0.91), with a relative risk of 0.97 (95% CI, 0.58 to 1.62). The incidence of death or myocardial infarction was 3.2% in the abciximab group and 3.0% in the placebo group (P=0.47).

Conclusions—The findings of this study do not support a significant impact of abciximab on the risk of death and myocardial infarction in diabetic patients undergoing percutaneous coronary interventions after pretreatment with a 600-mg loading dose of clopidogrel at least 2 hours before the procedure. The present findings suggest, however, that abciximab reduces the risk of restenosis in diabetic patients receiving coronary bare metal stents. (Circulation. 2004;110:3627-3635.)

Key Words: coronary disease ■ diabetes mellitus ■ platelets ■ restenosis ■ stents

Diabetes is a major risk factor for atherosclerosis.1 Diabetes not only increases the risk of development of atherosclerotic coronary artery disease2 but also portends an adverse prognosis in patients with coronary artery disease who undergo percutaneous or surgical coronary interventions.3 In particular, the outcome of diabetic patients after percutaneous coronary interventions is markedly compromised by an excessive risk of thrombosis and restenosis.4 Increased atherosclerotic burden, endothelial dysfunction, hypercoagulability, an elevated inflammatory state, and enhanced proliferative response are considered possible mechanisms underlying the worsened outcome of diabetic patients after percutaneous coronary interventions.6

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Platelets from diabetic patients demonstrate increased activation and aggregation in response to shear stress and agonists for aggregation7–9 and may play a crucial role in the development of ischemic complications after percutaneous coronary interventions. Potent antiplatelet drugs may have a major favorable impact on the clinical outcome in diabetic patients, especially in those undergoing percutaneous coro-
nary interventions. In fact, the use of glycoprotein IIb/IIIa inhibitors as an adjunct therapy during percutaneous coronary interventions has enabled an overall improved outcome of patients and in particular the subset of patients with diabetes mellitus. In 3 randomized trials, the combined incidence of death or myocardial infarction at 6 months after percutaneous coronary intervention was reduced by 45% to 62% by glycoprotein IIb/IIIa inhibitors in the subgroup of patients with diabetes. One of these drugs, abciximab, has also been associated with a reduction of restenosis as shown by an analysis restricted to a subset of 92 diabetic patients with follow-up angiography. Definitive conclusions about the true value of glycoprotein IIb/IIIa inhibitors in diabetic patients undergoing percutaneous coronary intervention are, however, hampered by the fact that no dedicated randomized trials have been conducted thus far to address this issue in diabetic patients and that in nearly all the previous trials, pretreatment with thienopyridines had not been required. Some data suggest that the benefit provided by glycoprotein IIb/IIIa inhibitors decreases when patients are adequately pretreated with thienopyridines. Recent evidence indicates that a 600-mg loading dose of clopidogrel allows achievement of a pronounced antiplatelet effect within 2 hours. In the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) study, abciximab did not confer additional clinical benefit when given to patients who had been pretreated with a 600-mg loading dose of clopidogrel before percutaneous coronary intervention. However, insulin-treated diabetic patients were excluded from the ISAR-REACT trial. We designed the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) Study to evaluate whether abciximab has a favorable impact on the outcome of diabetic patients undergoing elective percutaneous coronary intervention after pretreatment with a 600-mg dose of clopidogrel.

Methods

Patients

All patients were enrolled in 3 German hospitals: Deutsches Herz-Zentrum and 1 Medizinische Klinik in Munich and Medizinische Klinik I in Garmisch-Partenkirchen. Diabetic patients with coronary artery disease were eligible for this study if they were to undergo elective percutaneous coronary intervention in native coronary vessels between January 2001 and October 2003 and had been pretreated with 600 mg clopidogrel at least 2 hours before intervention. Patients were excluded if they had had a myocardial infarction within the prior 14 days; if they had unstable angina with ST-segment changes of $0.1 \text{mV}$ in at least 2 ECG leads at rest and/or troponin-T level $>0.03 \text{ng/mL}$; if the target lesion was in a venous bypass graft; if they had a chronic occlusion (older than 3 months); if the target lesion contained angiographically visible thrombus; or if patients had a left ventricular ejection fraction $<30\%$, hemodynamic instability, pericarditis, malignancy, a stroke in the prior 3 months, active bleeding or bleeding diathesis, recent trauma or major surgery in the last month, a suspected aortic dissection, oral anticoagulation therapy, severe uncontrolled hypertension $>180 \text{ mm Hg}$, hemoglobin $<100 \text{ g/L}$ or hematocrit $<34\%$, platelet count $<100 \times 10^9/\text{L}$ or platelet count $>600 \times 10^9/\text{L}$, known allergic reaction to the study medication, had received a glycoprotein IIb/IIIa inhibitor within 14 days, or were pregnant (present or suspected). All patients provided written informed consent for participation in the study, and the study protocol was approved by the institutional ethics committee.

Study Protocol

Patients of both study groups received clopidogrel 600 mg at least 2 hours before the percutaneous coronary intervention. They also received 500 mg of aspirin. After the decision to perform a percutaneous coronary intervention but before the guidewire had crossed the lesion, patients were randomized in a double-blind manner with the use of sealed envelopes containing the randomization sequence for each participating center. Patients in the abciximab group received abciximab (0.25 mg/kg bolus, followed by 0.125 $\mu g/kg \text{ per minute}$ [maximum of $10 \mu g/\text{min}$ infusion for 12 hours]) along with 70 U/kg of heparin. Patients in the placebo group received a placebo bolus and infusion of 12 hours and a bolus of heparin (140 U/kg). Double blinding was achieved with the use of vials that appeared similar in the 2 groups.

Coronary stenting was the target percutaneous coronary interventional according to protocol. Procedures completed with a residual diameter stenosis of the target lesion of $\geq 30\%$ or Thrombolysis In Myocardial Infarction (TIMI) flow grade $<3$ in the target vessel were considered unsuccessful. Postinterventional therapy included aspirin 200 mg indefinitely, clopidogrel 75 mg twice a day until discharge but no longer than 3 days, followed by daily administration of 75 mg for at least 6 months as indicated, as well as other cardiac medications believed to be required by the patient’s physician. The protocol provided for the performance of ECGs and collection of blood samples for determination of creatine kinase and its MB isoenzyme, hemoglobin, and platelet count every 8 hours for the first 24 hours after the procedure and daily afterward, until discharge. The same assay was used for the laboratory determination of creatine kinase and its MB isoenzyme in the 3 participating centers. All patients were asked at the time of enrollment to return to hospital at 6 to 8 months for follow-up angiography. A telephone interview was performed at 30 days and 12 months after randomization, and patients with complaints believed to possibly represent cardiac problems were seen in an outpatient clinic for a complete clinical, ECG, and laboratory checkup.

Quantitative Coronary Angiography Evaluation

Coronary angiograms at baseline, after completion of the procedure, and at follow-up were digitally recorded and sent for assessment to the Quantitative Angiographic Core Laboratory (Deutsches Herzzentrum, Munich, Germany). Analyses were performed by staff unaware regarding to which treatment arm the patient had been assigned. Digital angiograms were analyzed with the use of an automated edge detection system (CMS, Medis Medical Imaging Systems). All measurements were performed on cineangiograms recorded after intracoronary nitroglycerin administration. The same projections were used at baseline and at the time of follow-up angiography. The contrast-filled nontapered catheter tip was used for calibration. The quantitative parameters that were measured included the reference diameter of the vessel, the minimal lumen diameter, and percent diameter stenosis (difference between the reference diameter and minimal lumen diameter divided by the reference diameter and multiplied by 100). For patients who received stents, the quantitative analysis was performed in the “in-segment” area including the stented segment as well as both 5-mm margins proximal and distal to the stent (in-segment analysis).

Definitions and Study End Points

Diabetes mellitus was defined as active treatment with insulin or an oral hypoglycemic agent; for patients diagnosed with diabetes who were on dietary therapy alone, documentation of an abnormal fasting blood glucose or glucose tolerance test based on the World Health Organization criteria was required for enrollment in the trial. Multivessel disease was defined as the presence of angiographically significant lesions ($>50\%$ lumen narrowing) in $\geq 2$ major epicardial coronary arteries.
The primary end point of the study was the cumulative incidence of death from any cause and myocardial infarction during the first 12 months after randomization. The diagnosis of myocardial infarction was based on either the development of new pathological Q waves in ≥2 contiguous ECG leads or an elevation of creatine kinase or its MB isoenzyme to ≥2 contiguous ECG leads or an elevation of creatine kinase or its MB isoenzyme to ≥3 times the upper limit of normal in ≥2 samples. Within the same period, we also assessed the need for revascularization (aortocoronary bypass surgery or percutaneous coronary reintervention). The secondary end point of the trial was the incidence of binary angiographic restenosis, defined as a diameter stenosis of ≥50% on follow-up angiography on the basis of the in-segment analysis. In addition, we assessed the incidence of target lesion revascularization due to angiographic restenosis and symptoms or signs of ischemia.

The safety of the study medications was assessed by the 30-day incidence of major and minor bleeding, profound thrombocytopenia (<20 x 10^9/L), and need for transfusion. Major and minor bleeding was defined according to the TIMI criteria. A bleeding complication was defined as major if it was intracranial or if clinically significant overt signs of hemorrhage were associated with a drop in hemoglobin of >50 g/L (or, when hemoglobin was not available, an absolute drop in hematocrit of 15%). Minor bleeding was defined as clinically overt hemorrhage (including that seen on imaging) associated with a fall in hemoglobin of 30 to <50 g/L (or, when hemoglobin was not available, a fall in hematocrit of 9% to <15%).

All events were adjudicated and classified by an event adjudication committee blinded to the assigned treatment.

### Statistical Analysis

In the randomized trials on the value of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions, a 6-month combined incidence of death and myocardial infarction of 10.6% to 14.8% has been reported in diabetic patients of the placebo groups and of 5.6% to 9.4% in diabetic patients of the glycoprotein IIb/IIIa inhibitor groups. We assumed a 1-year incidence of the primary end point of 14% in the placebo group and of 7.5% in the abciximab group, which corresponds to a risk reduction of 50% with abciximab. The design of the trial was to have 80% power for detecting this reduction at an α-level of 0.05. On this basis, 350 patients were needed in each group.

All analyses were performed in a blinded manner regarding the randomly assigned treatment. Unblinding of the study groups was done after completion of the statistical analyses. No patient required unblinding because of clinical needs, and no crossovers occurred. The data are presented as mean±SD, median (25th, 75th percentiles), or counts or proportions (percentage). The differences between continuous data. We calculated the relative risk (RR) (with 95% CI) connected with assignment to abciximab. Prespecified secondary analyses addressed the subset of patients on insulin therapy. Statistical significance was accepted for a 2-tailed P<0.05.

### Results

Baseline characteristics of the patients are displayed in Table 1. Of note, the mean age of the study population was 68 years, 43% had class III or IV angina, 83% had multivessel disease, 34% had a history of myocardial infarction, and 29% were treated with insulin. Angiographic characteristics of the lesions and procedural variables are displayed in Table 2. The most frequent type of intervention used was placement of bare stents, followed by placement of drug-eluting stents and
plain balloon angioplasty. Table 3 shows the medications administered at discharge.

Four patients (1.1%) in the abciximab group and 3 patients (0.9%) in the placebo group incurred a major bleed (P=0.99). The incidence of minor bleeding was 3.4% (12 patients) in the abciximab group and 1.4% (5 patients) in the placebo group (P=0.09). Thus, 4.6% (16 patients) in the abciximab group and 2.3% (8 patients) in the placebo group had major or minor bleeding (P=0.1). Major bleeding was not observed in the 2 patients who required aortocoronary bypass surgery within 5 days from randomization. Profound thrombocytopenia occurred in 4 patients (1.1%) in the abciximab group versus none in the placebo group (P=0.12). Transfusion of blood products was required in 8 patients (2.3%) of the abciximab group and 2 patients (0.6%) of the placebo group (P=0.11). None of the patients suffered a hemorrhagic stroke.

**TABLE 2. Angiographic and Procedural Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (n=453)</th>
<th>Placebo (n=466)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of treated lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery, n (%)</td>
<td>9 (2)</td>
<td>10 (2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Left anterior descending coronary artery, n (%)</td>
<td>183 (40)</td>
<td>189 (41)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery, n (%)</td>
<td>144 (32)</td>
<td>141 (30)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery, n (%)</td>
<td>110 (24)</td>
<td>123 (26)</td>
<td></td>
</tr>
<tr>
<td>Bypass vein graft, n (%)</td>
<td>7 (2)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Complex (type B2/C) lesions, n (%)</td>
<td>309 (68)</td>
<td>327 (70)</td>
<td>0.52</td>
</tr>
<tr>
<td>Total occlusions, n (%)</td>
<td>28 (6)</td>
<td>24 (5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Restenotic lesions, n (%)</td>
<td>29 (6)</td>
<td>41 (9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.3±7.0</td>
<td>13.0±7.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Minimal lumen diameter before intervention, mm</td>
<td>1.0±0.5</td>
<td>1.0±0.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Diameter stenosis before intervention, %</td>
<td>62.8±15.5</td>
<td>63.5±15.9</td>
<td>0.49</td>
</tr>
<tr>
<td>Treatment device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare stents, n (%)</td>
<td>363 (80)</td>
<td>373 (80)</td>
<td>0.97</td>
</tr>
<tr>
<td>Drug-eluting stents, n (%)*</td>
<td>47 (10)</td>
<td>46 (10)</td>
<td>0.80</td>
</tr>
<tr>
<td>Balloon angioplasty, n (%)</td>
<td>43 (10)</td>
<td>47 (10)</td>
<td>0.76</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>12.0±2.7</td>
<td>12.9±2.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Maximal balloon-to-vessel ratio</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>0.93</td>
</tr>
<tr>
<td>Minimal lumen diameter after intervention, mm</td>
<td>2.6±0.6</td>
<td>2.6±0.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Diameter stenosis after intervention, %</td>
<td>7.8±14.0</td>
<td>8.7±15.2</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are presented as number of lesions (%) or mean±SD.

*Of the 93 lesions treated with drug-eluting stents, 89 were treated with Cypher stents (Cordis, Johnson & Johnson) and 4 with Taxus stents (Boston Scientific).

**TABLE 3. Medications Prescribed at Discharge**

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (n=351)</th>
<th>Placebo (n=350)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, n (%)</td>
<td>344 (98)</td>
<td>343 (98)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>351 (100)</td>
<td>350 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE inhibitors, n (%)</td>
<td>317 (90)</td>
<td>318 (91)</td>
<td>0.81</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>327 (93)</td>
<td>330 (94)</td>
<td>0.54</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>300 (86)</td>
<td>307 (88)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%).

**Clinical Outcome**

Thirty-day adverse event rates are shown in Table 4. During this interval, the combined incidence of death, myocardial infarction, or urgent revascularization was 5.7% (20 patients) in the abciximab group and 4.3% (15 patients) in the placebo group (P=0.39).

One-year clinical follow-up was complete in all but 24 patients (3.4%): 11 in the abciximab group and 13 in the placebo group were lost to follow-up. The median follow-up interval in these 24 patients was 7.1 months (25th, 75th percentiles: 3.7, 9.3 months). The cumulative incidence of death and myocardial infarction in the 1 year after enrollment was 8.3% (29 patients) in the abciximab group and 8.6% (30 patients) in the placebo group (P=0.91; Figure 1). Thus, abciximab was associated with a RR of death or myocardial infarction of 0.97 (95% CI, 0.58 to 1.62). Table 4 shows the adverse events observed in the 2 groups in detail. Notably, the 1-year mortality was 4.8% (17 patients) in the abciximab group and 5.1% (18 patients) in the placebo group (P=0.86), and there were no differences in the incidence of myocardial infarction and aortocoronary bypass surgery. In insulin-treated patients, the incidence of the primary end point was 12.0% in the abciximab group and 14.3% in the placebo group (P=0.66), and mortality was 9.1% in the abciximab group and 11.3% in the placebo group (P=0.62).

**Restenosis**

Eighteen patients were deemed ineligible for follow-up angiography as a result of unsuccessful procedure, death, or
urgent revascularization within 30 days: 10 in the abciximab group and 8 in the placebo group. Of the 683 eligible patients, 546 patients (80%) had follow-up angiography at a median of 197 days (25th, 75th percentiles: 181, 220 days) after randomization. Table 5 shows the results obtained at follow-up angiography. Both continuous measures of restenosis, minimal lumen diameter and diameter stenosis, indicated significantly less luminal renarrowing in abciximab-treated patients.

The secondary end point, the incidence of angiographic restenosis, was achieved in 28.9% in the abciximab group and 37.8% in the placebo group ($P_{H11005} = 0.01$; Figure 2), which yielded a RR of 0.76 (95% CI, 0.62 to 0.94). The incidence of insulin-treated patients, the incidence of angiographic restenosis was 32.7% in the abciximab group and 41.5% in the placebo group ($P_{H11005} = 0.19$). In lesions treated with bare stents, the incidence of angiographic restenosis was 31.9% in the abciximab group and 40.2% in the placebo group ($P_{H11005} = 0.04$). In lesions treated with drug-eluting stents, the incidence of angiographic restenosis was 7.3% in the abciximab group and 4.9% in the placebo group ($P_{H11005} = 1.0$).

### Discussion

Patients with diabetes have not experienced the favorable decline in cardiovascular mortality observed in the US population at large. Among insulin-treated patients, the incidence of angiographic restenosis was 32.7% in the abciximab group and 41.5% in the placebo group ($P_{H11005} = 0.19$). In lesions treated with bare stents, the incidence of angiographic restenosis was 31.9% in the abciximab group and 40.2% in the placebo group ($P_{H11005} = 0.04$). In lesions treated with drug-eluting stents, the incidence of angiographic restenosis was 7.3% in the abciximab group and 4.9% in the placebo group ($P_{H11005} = 1.0$).

**Figure 1. One-year cumulative incidence of the primary end point, death or myocardial infarction, in the abciximab and placebo groups.**

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (n=351)</th>
<th>Placebo (n=350)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>3 (0.9)</td>
<td>3 (0.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>15 (4.3)</td>
<td>11 (3.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Q wave (%)</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-Q wave (%)</td>
<td>14 (4.0)</td>
<td>9 (2.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Death or myocardial infarction (%)</td>
<td>18 (5.1)</td>
<td>14 (4.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Urgent revascularization (%)</td>
<td>4 (1.1)</td>
<td>5 (1.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Death or myocardial infarction or urgent revascularization (%)</td>
<td>20 (5.7)</td>
<td>15 (4.3)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

TABLE 4. Cumulative Frequency of Cardiac Events At 30 Days and 1 Year

Data are presented as number of patients (%). *Five patients had both percutaneous coronary revascularization and aortocoronary bypass surgery.

Figure 1. One-year cumulative incidence of the primary end point, death or myocardial infarction, in the abciximab and placebo groups.
the risk of thrombosis and restenosis in patients undergoing elective coronary stenting after pretreatment with a 600-mg loading dose of clopidogrel at least 2 hours before the procedure. The 2 major findings of this study are that abciximab did not reduce the cumulative risk of death or myocardial infarction during the year after the intervention, but it did significantly reduce the risk of restenosis. An important issue to be considered before trying to draw conclusions from the findings of this trial is that related to sample size. The trial was designed to have 80% power to discern a 50% risk reduction with abciximab, assuming a 10.8% overall incidence of the primary end point. With the actual 8.4% incidence of the primary end point, the trial had a 69% power to detect the assumed risk reduction. The loss of 11% power, which should be acknowledged as a limitation of this trial, is due to the lower than expected incidence of the primary end point in the placebo group. This may be related to the pretreatment with 600 mg of clopidogrel. Recent evidence demonstrates that a loading dose of 600 mg of clopidogrel leads to a more rapid platelet inhibition compared with 300 mg17 and may obviate the need for abciximab during elective percutaneous coronary interventions in patients at low to intermediate risk.18 It is not known whether other loading regimens of clopidogrel, including the 300-mg dose, provide a clinical efficacy comparable to that demonstrated for 600 mg of clopidogrel given at least 2 hours before the procedure.

The administration of abciximab in addition to the administration of a 600-mg loading dose of clopidogrel appeared to be safe in patients with diabetes who undergo a percutaneous coronary intervention, as it did in the ISAR-REACT trial.25 The incidences of major bleeding of 1.1% and of minor bleeding of 3.4% in this study are comparable to those of 0.7% and 5.0%, respectively, observed in the subset of diabetics in a previous trial of abciximab.25 Transfusion of blood products was needed in 2.3% of the patients in the abciximab group, which is within the range of 1.4% to 2.8% reported for patients assigned to stenting plus glycoprotein IIb/IIIa inhibitors in previous randomized trials.13,14,26,27 These safety data are even more important when the heparin regimen used in the present trial is considered. In the abciximab group, we used a heparin dose of 70 U/kg, which corresponds to the upper limit defined in current guidelines (50 to 70 U/kg).28 In the placebo group, we used a larger heparin bolus than is traditionally used in the United States (140 versus 100 U/kg),13 but, at the same time, there was no activated clotting time guidance, and no additional heparin doses were administered during the procedure, as was often the case in the placebo arms of previous randomized trials.29 It is standard practice in the centers participating in this study but also in many centers in Europe to not monitor the activated clotting time during percutaneous coronary interventions.

The primary end point in this trial was assessed during 1 year after randomization, an interval that is longer than that used for the primary end point in previous trials of glycoprotein IIb/IIIa inhibitors. Our intention was to avoid missing a possible incremental benefit of abciximab in hard end points over time, as has been the case in several prior studies.10,30 The use of an end point confined to the long-term incidence of death or myocardial infarction has been advocated for randomized trials of glycoprotein IIb/IIIa inhibitors in diabetics to enable assessment of the durability of benefit after 30 days with regard to acute ischemic events.11 The overall 1-year mortality in the diabetic population included in this trial was 5% and was similar in the 2 treatment arms. In a pooled analysis of diabetic patients included in 3 randomized placebo-controlled trials of percutaneous coronary interventions examining the benefits of abciximab, Bhatt et al10 found a 1-year mortality of 2.5%. However, the patients analyzed in the latter study10 were aged 60 years on average, ie, 7.5 years younger than the patients of the present study, which undoubtedly contributes to the difference in mortality. In a randomized trial comparing coronary stenting with aortocoronary bypass surgery, the diabetic patients assigned to coronary stenting were aged 62 years on average, received abciximab only rarely (<4%), and had a 1-year mortality of 6.3%.24

### Table 5. Angiographic and Clinical Restenosis

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (n=349)</th>
<th>Placebo (n=362)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>1.73±0.78</td>
<td>1.58±0.84</td>
<td>0.02</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>37.6±24.2</td>
<td>42.5±26.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Angiographic restenosis, n (%)</td>
<td>101 (28.9)</td>
<td>137 (37.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Target lesion revascularization, n (%)</td>
<td>81 (23.2)</td>
<td>110 (30.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are presented as number of lesions (%) or mean±1 SD.

Figure 2. Incidence of angiographic restenosis and target lesion revascularization in the abciximab and placebo groups.
We found no differences between the abciximab and placebo groups in the incidence of the primary end point, the combined incidence of death and myocardial infarction, or in either of its 2 components when analyzed separately. Because platelets play a key role in thrombotic complications after percutaneous coronary interventions, it may be speculated that the loading dose of 600 mg clopidogrel afforded sufficient platelet inhibition and that there was no incremental protection achieved by the additional use of abciximab. It is also possible that the incidence of ischemic complications might have been even lower in the group of abciximab had a full heparin dose been given in this group. Diabetic patients may require higher than the usual half dose of heparin advocated in combination with glycoprotein IIb/IIIa inhibitors to handle with their heightened prothrombotic state. In support of this is a previous analysis revealing that diabetic patients treated with abciximab showed a lower incidence of ischemic complications if treated with standard doses of heparin compared with reduced doses of heparin.31 In an attempt to explain the increased need of heparin in diabetic patients, the authors of the latter study invoked additional prothrombotic alterations induced by diabetes involving thromboxane biosynthesis and thrombin-antithrombin III complexes.31 A subsequent pooled analysis did not define an activated clotting time that helps to optimize the tradeoff between ischemic complications and bleeding in diabetic patients undergoing percutaneous coronary interventions under the coverage of glycoprotein IIb/IIIa blockers.28 The diabetic patients included in the abciximab group of the present trial received the standard reduced dose of heparin recommended by current guidelines28 and also used in previous trials including patients with and without diabetes mellitus.13,14,26 Therefore, we cannot say whether the results in the abciximab group would have been better with a higher dose of heparin such as that used in the placebo group of the present trial. Finally, the exclusion of diabetic patients with acute coronary syndromes from the present study likely reduced the chances of abciximab to show its superiority. As a precaution, we did not include patients with acute coronary syndromes in this first trial examining the value of abciximab in diabetic patients undergoing percutaneous coronary intervention after pretreatment with a high loading dose of clopidogrel.

An important finding of the present study was the 24% reduction in risk of restenosis by abciximab. Data on the impact of abciximab on the risk of restenosis in diabetic patients have been inconsistent and produced by either a subset of 92 patients with follow-up angiography after stenting12 or a dedicated 91-patient study with intravascular ultrasound.32 The explanation for the reduction in restenosis with abciximab is speculative. Prevention of mural thrombus formation by inhibition of platelet aggregation and blunting of production of inflammatory mediators by platelets have been invoked to explain the reduction of restenosis by abciximab.12 These actions may be of particular impact in diabetic patients in whom both platelet aggregation and production of inflammatory mediators by platelets are enhanced.6 However, clopidogrel also decreases the expression of inflammatory mediators such as P-selectin and CD40-ligand on the platelet surface,33 and this effect after 600 mg was stronger than after 300 mg.34 The possible mechanisms for a reduction in restenosis may not be accurate, however, because the incidence of restenosis in the placebo group of this study was not lower than the previously reported restenosis rates in diabetic patients in the preclotipogrel era.4 Therefore, whatever the mechanism by which restenosis was reduced by abciximab, it is not shared by clopidogrel. Abciximab cross-acts with the leukocyte integrins Mac-1, which mediate inflammation after arterial injury and are thought to be involved in restenosis.35–37 Abciximab is also able to antagonize the vitronectin (αβ₃) receptor on platelets and smooth muscle cells.38 This receptor is involved in neointimal hyperplasia,39 and its expression is increased in diabetes.40 Whether these extraplatelet actions of abciximab are responsible for the reduction in restenosis with abciximab is unknown.

The rate of target lesion revascularization was higher than that previously reported in some studies.11 This may reflect the impact of protocol-mandated follow-up angiography, which was not applied in previous trials of glycoprotein IIb/IIIa inhibitors13,14,26 and is known to increase the frequency of revascularization procedures. Opinion is divided on the value of routine follow-up angiography. However, we chose to include it in this study not only because of its superior ability to detect restenosis compared with noninvasive testing but also because routine follow-up angiography is believed by many to provide prognostic value. Patients with restenosis detected by routine follow-up angiography have an increased mortality over 4 years; some data suggest that reintervention in such patients improves prognosis.41 Drug-eluting stents have shown a conspicuous preventive effect on restenosis.42,43 Although no dedicated studies have assessed their specific role in patients with diabetes, analyses focused on this subset have suggested that diabetes continues to be a risk factor for restenosis after drug-eluting stent placement.42 The limited number of patients treated with drug-eluting stents in our trial does not permit us to draw conclusions on possible complementary effects of abciximab, and specific studies on this issue are needed. However, the reduction of restenosis by abciximab as shown in this trial puts this drug in the list of treatment options that seek to prevent restenosis in the high-risk subset of diabetic patients.

In conclusion, the findings of this study do not support a significant impact of abciximab on the risk of death and myocardial infarction in diabetic patients undergoing percutaneous coronary interventions after pretreatment with a 600-mg loading dose of clopidogrel at least 2 hours before the procedure. The present findings suggest, however, that abciximab reduces the risk of restenosis in diabetic patients receiving coronary bare metal stents.

Appendix
The organization of the ISAR-SWEET Study was as follows: Steering Committee: A. Schömig (chairman); A. Kastrati (principal investigator); Event Adjudication Committee: J. Dirschinger; H. Schüllern; J. Pache; Data Coordinating Center: J. Mehilli (director); H. Bollwein; A. Dreschler; M. Müller; C. Volmer; M. Hadamitzky; Angiographic Core Laboratory: A. Dibra (director); S. Piniek; S. Meier; Clinical Follow-up Center: H. Holle; F. Rodrigues; K. Hösl;
ISAR-SWEET Study Sites and Investigators: Germany: Deutsches Herzcentrum, Munich: H. Schüllenh (principal investigator); C. Schmitt; M. Gawaz; N. von Beckerath. 1 Medizinische Klinik rechts der Isar, Munich: J. Dirschinger (principal investigator); J. Pache; M. Seyfarth; M. Karch. Medizinische Klinik I, Garmisch-Partenkirchen: F. Dotzer (principal investigator); M. Fleckenstein; C. Glatthor.

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Disclosure
Dr A. Kastrati has received research grants from Medtronic. Dr H. Schüllenh has spoken at scientific symposia supported by Lilly Germany and has served on an Advisory Board of Lilly Germany; Dr P.B. Berger has received small amounts of research support from Bristol-Meyer Squibb/Sanoﬁ, Cordis/Johnson & Johnson, Merck, and Guilford; he currently serves on a Scientiﬁc Advisory Board for Guilford and Genentech and formally served on an advisory board for Bristol-Meyer Squibb/Sanoﬁ; he has spoken at scientiﬁc symposia supported by Bristol-Meyer Squibb/Sanoﬁ, Merck, Aventis, Guilford, and the Medicines Co. Dr Berger is the medical director and owns equity in Lumen, Inc. Dr A. Schöming has received research grants for the Department of Cardiology he directs from Bristol-Meyer Squibb, Lilly, Boston Scientiﬁc, Cordis/Johnson & Johnson, and Guidant.

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