Impact of Different Platelet Glycoprotein IIb/IIa Receptor Inhibitors Among Diabetic Patients Undergoing Percutaneous Coronary Intervention

Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) 1-Year Follow-Up

Marco Roffi, MD; David J. Moliterno, MD; Bernhard Meier, MD; Eric R. Powers, MD; Cindy L. Grines, MD; Peter M. DiBattiste, MD; Howard C. Herrmann, MD; Michel Bertrand, MD; Katherine E. Harris, PhD; Laura A. Demopoulos, MD; Eric J. Topol, MD; for the TARGET Investigators*

Background—The platelet glycoprotein IIb/IIa receptor inhibitor abciximab, a monoclonal antibody, has been shown to improve early and late outcomes among diabetic patients undergoing percutaneous coronary intervention (PCI). It is unknown whether small-molecule agents confer similar benefits.

Methods and Results—In 18 countries, 4809 patients undergoing PCI with stent implantation were randomized to tirofiban or abciximab. At the time of enrollment, patients were stratified according to diabetes status. As compared with non-diabetic patients, patients with diabetes (n=1117) showed similar 30-day ischemic outcomes, an increased incidence of any target vessel revascularization (TVR) at 6 months (10.3% versus 7.8%; P=0.008), and a trend toward higher 1-year mortality (2.5% versus 1.6%; P=0.056). Among diabetic patients randomized to tirofiban (n=560), the incidence of death, myocardial infarction (MI), or urgent TVR at 30 days was 6.2%, and among those randomized to abciximab (n=557) it was 5.4% (hazard ratio [HR] 1.16; P=0.540). At 6 months, the composite of death, MI, or any TVR occurred in 15.7% and in 16.9% of tirofiban and abciximab patients, respectively (HR 0.93; P=0.610). Any TVR occurred in 9.5% and 11.1%, respectively (HR 0.84; P=0.366). The 1-year mortality was 2.1% in the tirofiban group and 2.9% in the abciximab group (HR 0.74; P=0.436).

Conclusions—Among diabetic patients undergoing PCI, tirofiban and abciximab were associated with comparable event rates, including similar rates of 6-month TVR and 1-year mortality. These findings suggest that the non-glycoprotein IIb/IIa properties of abciximab do not translate into a discernible long-term clinical benefit among diabetic patients. (Circulation. 2002;105:2730-2736.)

Key Words: glycoproteins ■ stents ■ diabetes mellitus ■ platelets

Diabetes mellitus is associated with worse outcome after percutaneous coronary angioplasty and stenting.1-3 Compared with non-diabetic patients, those with diabetes have higher mortality rates, more exuberant restenosis, and greater de novo disease progression.1,3,4 Subgroup analyses of clinical trials have shown the platelet glycoprotein (GP) IIb/IIa receptor inhibitor abciximab to be particularly beneficial among diabetic patients undergoing coronary stenting, potentially influencing the restenotic process.5,6 Animal studies have supported the concept that the monoclonal antibody fragment abciximab may limit restenosis by inhibiting neo-intimal hyperplasia via blockade of the αvβ3 (vitronectin) integrin on smooth muscle cells.7-9 In addition, the greatest relative risk reduction in 1-year mortality provided by abcix-
tirofiban and abciximab among diabetic patients also applies to small-molecule agents, such as tirofiban, which display pure $\alpha_{IIb}\beta_3$ (GP IIb/IIIa) inhibition. In particular, it remains to be determined whether the non-GP IIb/IIIa properties of abciximab, such as vitronectin$^{11}$ or Mac-1 receptor inhibition,$^{12}$ favorably affect target vessel revascularization (TVR) or late mortality. The Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET)$^{13,14a}$ was performed to test whether tirofiban (Aggrastat, Merck) was comparable to abciximab (ReoPro, Johnson and Johnson) in patients undergoing non-emergent stent-based PCI. We report the outcome of the diabetic population enrolled in the trial to 1 year.

**Methods**

**Patients**

The design and methods of TARGET have been previously described.$^{13,14a}$ In brief, between December 1999 and August 2000, 4809 patients undergoing non-emergent PCI of a de novo or restenotic lesion in a native vessel or a bypass graft were enrolled. The protocol mandated intention to stent all treated sites. Patients were excluded in the presence of ST-segment elevation myocardial infarction (MI), cardiogenic shock, creatinine $>$2.5 mg/dL, bleeding diathesis, or life-limiting conditions. At time of enrollment, patients were stratified according to diabetes status to allow similar distribution of diabetic patients among the 2 treatment arms. Patients were classified as having diabetes based on history, and insulin requirements were recorded. Enrollment sites were located in North America, Australia, and 14 European countries.

**Medications**

All patients received aspirin before the procedure, and the administration of clopidogrel 300 mg orally at least 2 hours before cardiac catheterization was strongly recommended. Heparin was dosed to achieve an activated clotting time of $\geq$250 seconds. The study drug was administered immediately before revascularization in a double-blind, double-dummy manner. Accordingly, all patients received both the active formulation of one treatment and the placebo formulation of the other treatment. Tirofiban was administered as a 10 $\mu$g/kg bolus followed by a 0.15 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$ infusion for 18 to 24 hours, and abciximab was administered as 0.25 mg/kg bolus and 0.125 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$ infusion (maximum 10 $\mu$g/min) for 12 hours. Aspirin and clopidogrel were continued for 30 days, and long-term aspirin was recommended.

**End Points**

The primary endpoint of the trial was a composite of death, nonfatal MI, or urgent TVR at 30 days. The 6-month composite of death, MI, and any TVR rate, as well as the 1-year mortality, were prespecified secondary endpoints, and all data were collected prospectively. Death was defined as all-cause mortality. The definition of MI during index hospitalization and to 30 days has been described.$^{13}$ From 30 to 180 days, MI was defined by a 2-fold rise in the creatine kinase (CK)-MB isoform on 2 occasions or the appearance of new Q-waves on ECG. Any TVR was defined as either percutaneous revascularization or bypass surgery to a vessel that had been treated during the index procedure. The first event for each patient was recorded for the 30-day composite endpoint. Safety analysis included major and minor bleeding complications as defined in the Thrombolysis in Myocardial Infarction (TIMI) trials.$^{14b}$

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Diabetes n=1117</th>
<th>No Diabetes n=3692</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>Death</td>
<td>4 (0.4%)</td>
<td>18 (0.5%)</td>
<td>0.577</td>
</tr>
<tr>
<td></td>
<td>Non-fatal MI</td>
<td>59 (5.3%)</td>
<td>237 (6.4%)</td>
<td>0.174</td>
</tr>
<tr>
<td></td>
<td>Death/MI</td>
<td>62 (5.5%)</td>
<td>248 (6.7%)</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>Urgent TVR</td>
<td>5 (0.4%)</td>
<td>31 (0.8%)</td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>Death/MI/Urgent TVR</td>
<td>65 (5.8%)</td>
<td>261 (7.1%)</td>
<td>0.153</td>
</tr>
<tr>
<td>6 months</td>
<td>Death</td>
<td>19 (1.7%)</td>
<td>32 (0.9%)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Non-fatal MI</td>
<td>72 (6.4%)</td>
<td>278 (7.5%)</td>
<td>0.231</td>
</tr>
<tr>
<td></td>
<td>Death/MI</td>
<td>88 (7.9%)</td>
<td>298 (8.1%)</td>
<td>0.824</td>
</tr>
<tr>
<td></td>
<td>Any TVR</td>
<td>115 (10.3%)</td>
<td>287 (7.8%)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Death/MI/TVR</td>
<td>182 (16.3%)</td>
<td>519 (14.1%)</td>
<td>0.082</td>
</tr>
<tr>
<td>1 year</td>
<td>Death</td>
<td>28 (2.5%)</td>
<td>60 (1.6%)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Values are given as n (%).

**Data Collection and Statistical Analysis**

Treatment analysis included all patients who received either study drug. Each enrollment center contacted patients for follow-up at 30 days, 6 months, and 1 year. When relevant, other medical records were collected (eg, death certificates, CK values, and revascularization reports). Endpoint events were investigator-reported, with 100% monitoring of source documentation. The double blinding of treatment assignment was maintained through 1-year follow-up. All endpoint events were reviewed and adjudicated by an independent Clinical Events Committee.

Percentages reported for demographic, procedural, and safety data were based on non-missing observations. Continuous baseline and procedural characteristics were reported as mean±SD. Categorical data were presented as percentages. Mortality at 1 year was reported as Kaplan-Meier estimates. Cox proportional-hazards model was used to calculate hazard ratios (HR) and CI based on time to event. The same method was used to obtain probability values for the primary endpoint, subgroup analyses, and secondary endpoints, as well as to test the interaction of diabetic status with treatment. Comparisons of TIMI bleeding events were performed using Fisher’s exact test. No adjustments were made for multiple statistical comparisons, and $P<0.05$ was considered statistically significance.

**Results**

**Treatment and Outcome According to Diabetes Status**

Of the 4809 patients enrolled in the trial, 1117 patients (23%) had diabetes, and follow-up at 1 year was available for 99% of patients. When compared with non-diabetic patients, those with diabetes had comparable event rates at 30 days, higher mortality and TVR rates at 6 months, and a trend toward higher mortality at 1 year (Table 1).

Stratification according to diabetes status at enrollment led to uniform distribution of diabetic patients to tirofiban (n=560) and abciximab (n=557) treatment. Diabetic patients treated with tirofiban versus abciximab had similar baseline and procedural characteristics (Tables 2 and 3). TIMI major bleeding events occurred in 0.5% of patients randomized to tirofiban and in 0.7% of patients randomized to abciximab ($P=0.725$). Minor bleeding was observed in 3.6% and 5.0% of cases, respectively ($P=0.249$). At 30 days, the incidence of ischemic events was similar (Table 4), and the composite of death, MI, or urgent TVR occurred in 6.2% of patients in the
tirofiban and 5.4% of patients in the abciximab group
(HR 1.16; 95% CI 0.71 to 1.89; P = 0.540). The outcomes
among diabetic patients in the 2 treatment arms remained
comparable at 6 months (Table 5). The triple endpoint (death,
MI, or any TVR) occurred in 15.7% of patients in the
tirofiban group and in 16.9% of patients in the abciximab
group (HR 0.93; 95% CI 0.69 to 1.24; P = 0.610). The
incidence of TVR was 9.5% and 11.1%, respectively (HR
0.84; 95% CI 0.59 to 1.22; P = 0.366). Twelve diabetic
patients (2.1%) died at 1 year in the tirofiban group and 16
patients (2.9%) died in the abciximab group (HR 0.74; 95%
CI 0.35 to 1.57; P = 0.436; Figure 1).

Among non-diabetic patients (n=3692), those receiving
tirofiban had higher events rates at 30 days compared with
those receiving abciximab; the incidence of death, MI, or
urgent TVR in the 2 groups was 7.9% and 6.2%, respectively
(HR 1.29; 95% CI 1.01 to 1.64; P = 0.043). At 6 months,
14.6% of patients in the tirofiban group and 13.5% of patients
in the abciximab group had an ischemic event (HR 1.08; 95%
CI 0.91 to 1.29; P = 0.355). The incidence of any TVR was
similar between the 2 groups (7.7% and 7.9%, respectively).
At 1 year, the mortality rate was 1.8% and 1.4%, respectively
(HR 1.32; 95% CI 0.79 to 2.20; P = 0.288; Figure 2). No
significant interaction was observed between diabetes status
and treatment (P = 0.719 and P = 0.362 for the composite
endpoint at 30 days and 6 months, respectively; P = 0.214 for
mortality at 1-year).

**Treatment and Outcome According to Insulin Treatment**

Overall, diabetic patients treated with insulin (n=503) and
those not receiving insulin (n=614) had similar outcomes. The
30-day incidence of death, MI, or urgent TVR was 5.6% and
6.0% (P = 0.764), and at 6 months the death, MI, or any TVR
composite occurred in 15.9% and 16.6% of patients
(P = 0.789), respectively. At 1 year, the mortality rate was
2.8% and 2.3% (P = 0.604), respectively.

Among patients on insulin, the composite endpoint of
death, MI, or urgent TVR occurred in 8.1% in the tirofiban
group and 3.1% in the abciximab group at 30 days (Figure 3).
The difference reached statistical significance (HR 2.65; 95%
CI 1.17 to 6.02; P = 0.020) and was driven by periprocedural
MI, which occurred in 6.5% of patients randomized to
tirofiban and in 2.3% of patients randomized to abciximab
(HR 2.79; 95% CI 1.09 to 7.14; P = 0.032). At 6 months,
the difference in the triple endpoint was no longer significant
(17.4% versus 14.4%, HR 1.25; 95% CI 0.81 to 1.94;
P = 0.317). At 1-year, the mortality was 2.0% and 3.5%,
respectively (HR 0.58; 95% CI 0.19 to 1.73; P = 0.329).

Among diabetic patients not receiving insulin, the inci-
dence of death, MI, or TVR at 30 days was 4.8% in the
tirofiban group and 7.3% in the abciximab group (HR 0.65;
95% CI 0.34 to 1.26; P = 0.203; Figure 3). At 6 months,
the incidence of the combined endpoint was 14.5% and 18.9%,
respectively (HR 0.73; 95% CI 0.50 to 1.08; P = 0.118). The
1-year mortality was 2.2% in the tirofiban group and 2.3% in
the abciximab group (HR 0.95; 95% CI 0.33 to 2.70;
P = 0.920).

**Discussion**

Previous clinical trial work from our group and others has
substantiated the benefit of abciximab compared with placebo
for diabetic patients undergoing PCI.6,10 It has remained
certain, however, whether small-molecule platelet GP IIb/
IIIa receptor inhibitors would achieve a similar benefit. In the
TARGET trial, which included the largest reported cohort of

---

**TABLE 2. Baseline Characteristics Among Diabetic Patients According to Treatment Assignment**

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban n=560</th>
<th>Abciximab n=557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3±10</td>
<td>63.2±10</td>
</tr>
<tr>
<td>Female, %</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>92.4±20</td>
<td>90.5±20</td>
</tr>
<tr>
<td>White, %</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Family history of coronary disease</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td>History of smoking</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Percutaneous revascularization</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Indication for coronary intervention, %</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Other</td>
<td>40</td>
<td>35</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as means±SD. P=NS for all comparisons.

---

**TABLE 3. Procedural Characteristics Among Diabetic Patients According to Treatment Assignment**

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban n=560</th>
<th>Abciximab n=557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary target vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Bypass graft</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Restenotic vessel</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Thrombus present</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Lesion length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>10-20 mm</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Any atherectomy</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Median stent length</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Values are expressed as % or mm. P=NS for all comparisons.
diabetic patients undergoing coronary stenting, we found that tirofiban led to comparable results with respect to many endpoints when compared with abciximab, specifically to similar rates of clinical restenosis (any TVR) and late survival. With diabetic patients duly acknowledged as among those at highest risk for restenosis and late mortality after PCI, this finding has important clinical and biological implications.

**Diabetes and Early Outcome After PCI**

In vitro and ex vivo studies have shown that diabetic patients have increased platelet aggregability. In particular, diabetes mellitus has been associated with a larger pool of activated circulating platelets, a higher density of GP IIb/IIIa receptors per platelet, and a greater expression of platelet P-selectin and thrombospondin. These adhesion molecules are potential triggers of inflammatory response and thrombosis. Despite increased baseline platelet aggregability, the administration of abciximab has been shown to achieve a similar degree of platelet aggregation inhibition among diabetic and non-diabetic patients undergoing PCI.

In contrast to clinical expectation and data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT), diabetic patients enrolled in the TARGET trial had favorable outcomes at 30 days, with relatively fewer ischemic events as compared with non-diabetic patients (5.8% versus 7.1%; \( P = 0.153 \)). The lack of excess of ischemic complications, and in particular of periprocedural MI, observed among diabetic patients seems counterintuitive. However, similar findings were observed in the Eptifibatide in Planned Coronary Stent Implantation Trial (ESPRIT), such that at 30 days, diabetic patients had lower event rates than non-diabetic patients, both in the placebo and in the eptifibatide treatment arms. One plausible explanation for this discrepancy among the trials is that following the results of the Bypass Angioplasty Revascularization Investigation (BARI) and the Arterial Revascularization Therapy Study (ARTS), which showed a survival benefit associated with bypass surgery among diabetic patients with multivessel disease, the diabetic patients enrolled in ESPRIT and TARGET may have represented a subset with coronary anatomy more favorable for PCI. This observation remains speculative, however, as a comparison of demographic or anatomic characteristics among the trials’ diabetic populations has not been made. In addition, as TARGET was designed with 2 active treatment arms, no placebo group was available for comparison to the previous trials.

In TARGET, we observed that the use of tirofiban and abciximab among diabetic patients led to similar 30-day event rates, though the hazard ratio for the composite endpoint was consistent with the overall trial findings that favored abciximab. No significant interaction was detected between diabetic status and treatment.

### Integrin Receptors and Target Vessel Revascularization

Diabetes mellitus is associated with worse intermediate- and long-term outcomes after percutaneous coronary angioplasty and stenting as compared with non-diabetic patient outcomes. Characteristic among diabetic patients is the excess of TVR, a surrogate marker for angiographic restenosis. Intravascular ultrasound studies have shown that diabetic patients have more aggressive tissue proliferation, both in stented and non-stented lesions. Likewise, at long-term follow-up, the outcome of diabetic patients after PCI is marked by more rapid progression of native coronary artery disease than that in non-diabetics. As anticipated, the diabetic patients enrolled in TARGET had significantly higher

---

**TABLE 4. 30-Day Cardiac Events Among Diabetic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban n=560</th>
<th>Abciximab n=557</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 (0.5%)</td>
<td>1 (0.2%)</td>
<td>2.99</td>
<td>0.31–28.77</td>
<td>0.342</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>31 (5.5%)</td>
<td>28 (5.0%)</td>
<td>1.10</td>
<td>0.66–1.84</td>
<td>0.703</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>2 (0.4%)</td>
<td>3 (0.5%)</td>
<td>0.67</td>
<td>0.11–3.99</td>
<td>0.657</td>
</tr>
<tr>
<td>Death/MI</td>
<td>33 (5.9%)</td>
<td>29 (5.2%)</td>
<td>1.14</td>
<td>0.69–1.87</td>
<td>0.618</td>
</tr>
<tr>
<td>Death/MI/urgent TVR</td>
<td>35 (6.2%)</td>
<td>30 (5.4%)</td>
<td>1.16</td>
<td>0.71–1.89</td>
<td>0.540</td>
</tr>
</tbody>
</table>

**TABLE 5. 6-Month Cardiac Events Among Diabetic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban n=560</th>
<th>Abciximab n=557</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>8 (1.4%)</td>
<td>11 (2.0%)</td>
<td>0.72</td>
<td>0.29–1.78</td>
<td>0.471</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>39 (7.0%)</td>
<td>33 (5.9%)</td>
<td>1.17</td>
<td>0.74–1.86</td>
<td>0.500</td>
</tr>
<tr>
<td>TVR</td>
<td>53 (9.5%)</td>
<td>62 (11.1%)</td>
<td>0.84</td>
<td>0.59–1.22</td>
<td>0.366</td>
</tr>
<tr>
<td>PCI</td>
<td>37 (6.6%)</td>
<td>47 (8.4%)</td>
<td>0.77</td>
<td>0.50–1.19</td>
<td>0.241</td>
</tr>
<tr>
<td>CABG</td>
<td>19 (3.4%)</td>
<td>19 (3.4%)</td>
<td>0.99</td>
<td>0.52–1.87</td>
<td>0.973</td>
</tr>
<tr>
<td>Death/MI</td>
<td>46 (8.2%)</td>
<td>42 (7.5%)</td>
<td>1.09</td>
<td>0.72–1.65</td>
<td>0.698</td>
</tr>
<tr>
<td>Death/MI/TVR</td>
<td>88 (15.7%)</td>
<td>94 (16.9%)</td>
<td>0.93</td>
<td>0.69–1.24</td>
<td>0.610</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless otherwise noted.
TVR rates compared with non-diabetic patients. Nonetheless, the 6-month TVR observed in the present study (10.3%) is comparable to the rate reported among diabetic patients in the stent-abciximab group of EPISTENT (8.1%). This demonstrates that in the current PCI-stent-IIb/IIIa era, the low TVR rate observed in EPISTENT can be reproduced in a large-scale diabetic population.

Controversy over whether abciximab has anti-restenotic properties evolved from observed reductions in 6-month TVR among some, but not all, trials. The only prior PCI-stent-abciximab trial, EPISTENT, showed that the combination of abciximab and stenting was associated with a significant (51%) reduction in TVR at 6 months among diabetic patients. The hypothesis of an inhibitory effect of the drug on restenosis was supported by the angiographic substudy of the trial, which showed that among diabetic patients undergoing coronary stenting, randomization to abciximab was associated with a significant increase in net gain (the difference between minimal luminal diameter at follow-up and before intervention). Animal studies have reinforced the concept that the antibody fragment abciximab may play a role in restenosis prevention by inhibiting neointimal hyperplasia. Putative pathways involve inhibition of both the \( \alpha_{\text{IIb}} \beta_3 \) (GP IIb/IIIa) receptor, which is confined to platelets, and of the \( \alpha_v \beta_3 \) (vitronectin) receptor, which is heavily expressed by several cell lines, including endothelial cells, monocytes, and smooth muscle cells. Abciximab has been shown to directly inhibit smooth muscle cell migration and proliferation through binding of \( \alpha_v \beta_3 \) integrin of smooth muscle cells. Conversely, the small-molecule tirofiban, which binds exclusively to the \( \alpha_{\text{IIb}} \beta_3 \) receptor, has demonstrated no effect on smooth muscle cells in animal models or on angiographic restenosis in angioplasty substudies. Additional properties of abciximab include cross-reactivity with the leukocyte \( \alpha_v \beta_3 \) integrin (Mac-1), a mediator of inflammation after arterial injury, which may also be involved in restenosis. Despite the suggestive findings in EPISTENT and the plausible mechanistic explanations from animal studies, an intravascular ultrasound study designed to assess neointimal volume after PCI-stent failed to demonstrate a significant benefit from abciximab.

Among diabetic patients enrolled in TARGET, those randomized to tirofiban had a nonsignificant 16% lower TVR rate at 6 months compared with patients randomized to abciximab. Despite the limitation that TARGET was not an angiographic study, and acknowledging that TVR is only a surrogate marker of restenosis, our findings suggest that the non-GP IIb/IIIa properties of abciximab do not translate into a clinically relevant inhibition of the restenotic process.

Long-Term Mortality

In the EPISTENT trial, abciximab was associated with a significant overall mortality reduction at 1 year as compared with placebo (2.4% to 1.0%; \( P = 0.037 \)) among PCI-stent patients. In addition, a pooled analysis of the Evaluation of c7E3 in Preventing Ischemic Complications (EPIC), Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG), and EPISTENT data sets, found that diabetic patients specifically (n = 1462) derive a 44% 1-year mortality reduction associated with abciximab (4.5% to 2.5%; \( P = 0.031 \)). In TARGET, the diabetic patients enrolled were at a higher risk for death compared with non-diabetics at 6 months, and the trend persisted at 1-year. Up to 1 year, no difference in diabetic mortality was observed between the 2 agents. This suggests that the long-term mortality benefit of platelet GP IIb/IIIa receptor inhibitors among diabetic patients may not be linked to abciximab-specific effects.

Insulin Requirement and Outcome

Overall, diabetic patients on insulin and those not requiring insulin had similar outcomes at 30 days and 6 months, as well
as similar 1-year mortality rates. Among patients not treated with insulin, tirofiban and abciximab were associated with comparable event rates at 30 days and 6 months, as well as similar 1-year mortality rates. Among patients on insulin, those randomized to tirofiban had higher incidence of the triple endpoint at 30 days, driven by an excess of peri-procedural MI. This difference lost statistical significance at 6 months, and at 1-year the mortality rates were similar. The isolated significant benefit associated with abciximab in terms of peri-procedural MI among patients requiring insulin could be the result of chance or could indicate that these patients derive particular benefit from a presumably more potent and more broad (ie, non-GP IIb/IIIa mediated) platelet inhibition generated by abciximab. Although we do not have information regarding the etiology of diabetes among patients receiving insulin (type 1 insulin-sensitive versus type 2 insulin-resistant), the vast majority of the patients enrolled in the trial were likely to have type 2 diabetes. Insulin resistance appears to have a direct impact on hemostasis, as suggested by the correlation between insulin levels and both fibrinogen and plasminogen activator inhibitor (PAI)-1 levels. Further studies are needed to assess whether insulin resistance may be used to identify diabetic patients at highest thrombotic risk during PCI, and accordingly to guide future studies and specific treatments.

Limitations
This study is subject to the limitations of subgroup analysis because it was not powered to compare tirofiban with abciximab solely among diabetic patients. In addition, multiple statistical comparisons without adjustments were performed. This analysis, however, involves the largest reported cohort of diabetic patients undergoing coronary stenting. Moreover, the diabetic subgroup was prespecified in the study protocol for stratification at enrollment and statistical analysis. As TARGET was not an angiographic study, no conclusive statements can be made regarding differences between the 2 drugs with regard to restenosis. Based on TVR rates, however, it is unlikely that a clinically meaningful difference went undetected.

Conclusions
Within the first head-to-head comparison of 2 platelet GP IIb/IIIa inhibitors as adjunctive treatment for stent-based PCI, peri-procedural administration of the small-molecule tirofiban and the antibody fragment abciximab led to overall similar outcomes among diabetic patients. In particular, the comparable TVR and mortality rates observed between the 2 groups suggest that the non-GP IIb/IIIa properties of abciximab do not translate into a discernible long-term clinical benefit among diabetic patients.

References


Impact of Different Platelet Glycoprotein IIb/IIIa Receptor Inhibitors Among Diabetic Patients Undergoing Percutaneous Coronary Intervention: Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) 1-Year Follow-Up

Marco Roffi, David J. Moliterno, Bernhard Meier, Eric R. Powers, Cindy L. Grines, Peter M. DiBattiste, Howard C. Herrmann, Michel Bertrand, Katherine E. Harris, Laura A. Demopoulos and Eric J. Topol
for the TARGET Investigators*

_Circulation_. 2002;105:2730-2736; originally published online May 13, 2002;
doi: 10.1161/01.CIR.0000018123.02672.C7

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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:
http://circ.ahajournals.org/content/105/23/2730

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/