Thrombocytopenia Caused by Abciximab or Tirofiban and Its Association With Clinical Outcome in Patients Undergoing Coronary Stenting

Piera Angelica Merlini, MD; Marco Rossi, MD; Alberto Menozzi, MD; Silvia Buratti, MD; Danielle M. Brennan, MS; David J. Moliterno, MD; Eric J. Topol, MD; Diego Ardissino, MD

Background—Thrombocytopenia is a possible complication of treatment with glycoprotein (GP) IIb/IIIa antagonists during percutaneous coronary interventions, but it is not clear whether different GP IIb/IIIa inhibitors carry a different risk of thrombocytopenia, and its relation to clinical outcome is unknown.

Methods and Results—We analyzed data from the Do Tirofiban and Reopro Give Similar Efficacy Outcomes (TARGET) study, which compared the safety and efficacy of abciximab and tirofiban in patients undergoing coronary stenting. Platelets were measured at baseline and 6 and 24 hours after the beginning of treatment. Thrombocytopenia (nadir platelet count /10^10 cells/L) developed in 2.4% of patients treated with abciximab and 0.5% of those treated with tirofiban (P<0.001). The variables independently associated with thrombocytopenia were treatment with abciximab within the previous 6 months (OR, 4.4; 95% CI, 1.7 to 11.2), baseline creatinine levels of ≥0.8 mg/dL (OR, 3.8; 95% CI, 1.7 to 8.8), previous transient ischemic attack (OR, 3.2; 95% CI, 1.4 to 7.6), female gender (OR, 1.9; 95% CI, 1.2 to 3.1), and history of peripheral vascular disease (OR, 1.78; 95% CI, 1.0 to 3.1). Severe bleeding occurred more frequently in patients with thrombocytopenia (5.1% versus 0.7%, P=0.001), who also more frequently received blood transfusions (6.1% versus 1.4%, P=0.001). At the 30-day follow-up, 2.0% of patients with thrombocytopenia and 0.4% of those without (P=0.022) had died; myocardial infarction occurred in 9.13% versus 6.11% (P=NS); and target vessel revascularization occurred in 6.07% versus 0.60% (P<0.001).

Conclusions—During coronary stenting, abciximab and other risk factors are independently associated with thrombocytopenia. Regardless of the cause, thrombocytopenia is associated with more ischemic events, bleedings, and transfusions. (Circulation. 2004;109:2203-2206.)

Key Words: thrombosis ■ stents ■ anticoagulants ■ platelets

In patients undergoing percutaneous coronary interventions (PCIs), pharmacological blockade of the platelet glycoprotein (GP) IIb/IIIa receptor has emerged as a key strategy for improving clinical outcome. However, the increased use of GP IIb/IIIa antagonists has led to the associated hemorrhagic risk becoming a major safety concern. In particular, thrombocytopenia is a feared complication.

All parenteral GP IIb/IIIa antagonists have been associated with thrombocytopenia, with incidences ranging from 0.5% to 5.6%.1-5 The reported incidence in abciximab trials has been relatively higher, but precise assessment is confounded by differences in the agents (antibody versus synthetic, peptide versus nonpeptide), dose, duration of drug exposure, and nature of the coadministered agents. The Do Tirofiban and Reopro Give Similar Efficacy Outcomes (TARGET) trial prospectively randomized 4809 patients to intravenous abciximab (n=2411) or tirofiban (n=2398) during planned coronary stenting1 and thus provides an opportunity to directly compare the 2 GP IIb/IIIa inhibitors in terms of the development of thrombocytopenia and the associated clinical outcome.

Methods

Patients
TARGET was an international, double-blind, randomized trial involving 4809 patients of any age and either gender with stable coronary artery disease or an acute coronary syndrome who were scheduled to undergo PCI for lesions amenable to stent implantation. The inclusion and exclusion criteria, study interventions, and primary efficacy outcomes have been published elsewhere.3

Study Protocol
A double-blind, double-dummy design was used to randomize the patients to tirofiban (a 10-μg/kg IV bolus followed by an infusion of
then every 6 hours for 24 hours. (CK)-MB levels were determined 6 hours after the procedure and discontinuation at the end of the procedure. Creatine kinase clotting time was 250 seconds. The protocol suggested heparin procedure at a dose of no more than 70 U/kg; the target activated before the procedure. Heparin was administered at the start of the 300-mg loading dose of clopidogrel was recommended 2 to 6 hours within 24 hours of the procedure and 75 to 325 mg/d thereafter. A minute for 12 hours). All patients received 250 to 500 mg aspirin /H11021 (n=99)

<table>
<thead>
<tr>
<th></th>
<th>Thrombocytopenia</th>
<th>No Thrombocytopenia</th>
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<tbody>
<tr>
<td>Male, %</td>
<td>70.7</td>
<td>73.6</td>
<td>0.004</td>
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<tr>
<td>Median age (range), y</td>
<td>67 (45–89)</td>
<td>62 (26–90)</td>
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<td>White, %</td>
<td>92.9</td>
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<td>54.9</td>
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<tr>
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<td>84.7</td>
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<td>Previous MI, %</td>
<td>48</td>
<td>39.3</td>
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<tr>
<td>Previous CABG, %</td>
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<td>0.023</td>
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<td>Previous TIA, %</td>
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<td>Gastrointestinal disorders, %</td>
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<tr>
<td>History of peripheral vascular disease, %</td>
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<td>9.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Bleeding disorders, %</td>
<td>2</td>
<td>0.8</td>
<td>0.182</td>
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</tbody>
</table>

CAD indicates coronary artery disease; MI, myocardial infarction; and TIA, transient ischemic attack.

0.15 μg/kg per minute for 18 to 24 hours) or abciximab (a 0.25-mg/kg bolus followed by an infusion of 0.125 to 10 μg/kg per minute for 12 hours). All patients received 250 to 500 mg aspirin within 24 hours of the procedure and 75 to 325 mg/d thereafter. A 300-mg loading dose of clopidogrel was recommended 2 to 6 hours before the procedure. Heparin was administered at the start of the procedure at a dose of no more than 70 U/kg; the target activated clotting time was 250 seconds. The protocol suggested heparin discontinuation at the end of the procedure. Creatine kinase (CK)-MB levels were determined 6 hours after the procedure and then every 6 hours for 24 hours.

Efficacy End Points
The primary end point was the composite occurrence of death, myocardial infarction, or urgent target vessel revascularization (TVR) within 30 days. Myocardial infarction was considered periprocedural if it occurred within 48 hours of the procedure and there was an increase in CK-MB levels to >3 times the upper normal limit in 2 separate blood samples, regardless of whether it was accompanied by chest pain and/or ECG changes or new pathological Q waves. Nonprocedural myocardial infarction was considered to be the development of new Q waves or CK-MB levels of more than twice the upper normal limit on 2 occasions accompanied by chest pain and/or ECG changes >48 hours after the PCI.

Platelet Monitoring and Definitions
Hematological indexes were monitored at baseline and 6 and 24 hours after the procedure. If the platelet count dropped to <100×10^9 cells/L at any time, the test was immediately repeated by drawing blood into EDTA-free tubes, and if the decrease was confirmed, the study drug and heparin infusions were discontinued. Significant thrombocytopenia was defined as a platelet count of <100×10^9 cells/L or a decrease of ≥25% from baseline. Thrombocytopenia was defined as mild (50 to 100×10^9 cells/L platelets) or severe (<50×10^9 cells/L).

Bleeding End Points
Bleeding complications were categorized by bleeding site, and their severity was quantified according to the major and minor TIMI criteria. Major bleeding was defined as a decrease in hemoglobin of >5 g/dL (with or without an identified site and not associated with CABG), intracranial hemorrhage, or a spontaneous cardiac tamponade. Minor bleeding was defined as a decrease in hemoglobin of ≥3 but <5 g/dL, with bleeding from a known site (not associated with CABG), or spontaneous gross hematuria, hematemesis, or hemoptysis with a <3-g/dL decrease in hemoglobin levels.

The patients were clinically followed up after 30 days and 1 year. The human investigational review board at each site approved the protocol. All primary and secondary end points and safety measurements were adjudicated by an independent committee, blinded to the treatment allocation, which reviewed the original source documentation.

Statistical Analysis
Patients’ baseline characteristics were compared by use of χ^2 and Fisher’s exact tests for discrete variables and Wilcoxon’s rank-sum test for continuous variables. Logistic regression was used to model thrombocytopenia. The ORs and their corresponding 95% CIs are also provided. Linear splines were used for the continuous variables if there was no linear relationship to outcome. Bootstrapping techniques were used to validate the model. Kaplan-Meier estimates were calculated to compare the 30-day events, and log-rank tests were performed to test the Kaplan-Meier estimates. All hypothesis tests were 2 sided at the 5% significance level.

Results
Incidence of Thrombocytopenia and Its Relation to Clinical Characteristics
Thrombocytopenia occurred in 99 patients (2.9%); mild in 61 (60%) and severe in 38 (40%). The clinical characteristics of the patients developing thrombocytopenia are shown in the Table. They were older, weighed less, and had more frequently undergone previous CABG or suffered a previous stroke or transient ischemic attack. There was no difference in the clinical characteristics of patients developing severe or mild thrombocytopenia. Of the pre-PCI medications, abcix-
imab in the previous 6 months was observed more frequently in patients who developed thrombocytopenia (6.1% versus 1.4%, \(P=0.004\)). During hospitalization, patients who developed thrombocytopenia more frequently had heparin continued after the procedure (4% versus 1.3%, \(P=0.04\)) or restarted at the time of sheath removal (8.1% versus 2.2%, \(P=0.002\)).

The multivariate regression model for predictors of the development of thrombocytopenia showed that the independently associated variables were treatment with abciximab in the previous 6 months (OR, 4.4; 95% CI, 1.7 to 11.2), baseline creatinine levels of \(\geq 0.8\) mg/dL (OR, 3.88; 95% CI, 1.7 to 8.8), previous transient ischemic attack (OR, 3.2; 95% CI, 1.4 to 7.6), female gender (OR, 1.97; 95% CI, 1.2 to 3.1), and history of peripheral vascular disease (OR, 1.78; 95% CI, 1.02 to 3.11). The following clinical characteristics were independently associated with a protective effect: treatment with tirofiban (OR, 0.16; 95% CI, 0.09 to 0.29), pretreatment with heparin for no more than 4 hours (OR, 0.53; 95% CI, 0.29 to 0.93), family history of coronary artery disease (OR, 1.78; 95% CI, 1.02 to 3.11). The following clinical characteristics were independently associated with a protective effect: treatment with abciximab (OR, 0.53; 95% CI, 0.30 to 0.92), and a baseline platelet count of <220\(\times10^9\) cells/L (OR, 0.97; 95% CI, 0.96 to 0.98).

### Thrombocytopenia and Clinical Outcome

At the 30-day follow-up, death, myocardial infarction, or TVR had occurred in 6.6% of patients without and in 12.2% of those with thrombocytopenia (\(P=0.036\); death in 0.4% versus 2.0% (\(P=0.022\)), myocardial infarction in 6.1% versus 9.1% (\(P=NS\)), and TVR in 0.6% versus 6.1% (\(P<0.001\)).

The events occurred in 8.3% of patients with mild thrombocytopenia and 21.0% of those with severe thrombocytopenia: death in 0% versus 6.2% (\(P=0.05\)), myocardial infarction in 5.0% versus 21.0% (\(P=0.05\)), and TVR in 5.0% versus 9.4%.

### Bleeding Complications

Bleedings occurred in 24.6% of the patients without and 27.3% of those with thrombocytopenia (\(P=NS\), but severe bleeding occurred more frequently in the latter (5.1% versus 0.7%, \(P=0.001\)), who also more frequently received blood transfusions (6.1% versus 1.4%, \(P=0.001\)).

### Thrombocytopenia by Treatment

Thrombocytopenia occurred in 2.4% of the patients receiving abciximab and 0.5% of those receiving tirofiban (\(P<0.001\); 85% of the patients who developed thrombocytopenia had received abciximab. The clinical characteristics of the patients developing thrombocytopenia were similar in the 2 treatment groups (data not shown), except there was a higher prevalence of women among the patients developing thrombocytopenia on tirofiban (53% versus 25%, \(P=0.035\)). The mean nadir platelet count was lower in patients treated with abciximab (60\(\times10^9\) cells/L; minimum, 3.0\(\times10^9\) cells/L; maximum, 99\(\times10^9\) cells/L) than in those receiving tirofiban (67\(\times10^9\) cells/L; minimum, 24\(\times10^9\) cells/L; maximum, 97\(\times10^9\) cells/L). Profound thrombocytopenia developed in 0 patients receiving tirofiban compared with 22 (19%) treated with abciximab. In both groups, the mean time to onset of thrombocytopenia was 24 hours, with no cases occurring >48 hours after PCI. Tirofiban-induced thrombocytopenia resolved after a mean of 2.1 days (range, 1 to 6 days); abciximab-induced thrombocytopenia resolved after a mean of 4.5 days (range, 1 to 24 days).

Among patients who developed thrombocytopenia by day 30, there was no difference between those treated with abciximab and those treated with tirofiban in terms of death (11.9% versus 13.3%), myocardial infarction (8.4% versus 13.3%), or TVR (5.9% versus 6.6%).

### Discussion

Previous pooled analyses of thrombocytopenia complicating treatment with intravenous GP IIb/IIIa receptor inhibitors have suggested that the use of abciximab leads to more than twice the incidence of severe thrombocytopenia than placebo, whereas the use of eptifibatide or tirofiban does not cause any significant excess of thrombocytopenia.1–3 The present study, which directly compares abciximab and tirofiban, confirms that treatment with abciximab in patients undergoing coronary stenting procedures is associated with a higher incidence of thrombocytopenia.

### Pathophysiology of GP IIb/IIIa Thrombocytopenia

Little is known about the pathophysiological mechanisms leading to the thrombocytopenia induced by GP IIb/IIIa antagonists. One hypothesis suggests the critical presence of preexisting platelet surface antibodies. GP IIb/IIIa antagonists may induce a conformational change in the GP IIb/IIIa receptors on the platelet surface, thus leading to the expression of new epitopes that are recognized by the antibodies already present in the plasma. Alternatively, the recognized epitope may be formed by the receptor/antagonist complex. If a patient has preformed antibodies that cross-react with the new epitopes, the platelets may become coated with immunoglobulin and be removed from the circulation.

The difference in the rates of thrombocytopenia observed with abciximab and tirofiban may indicate that the new epitopes generated by the drugs are different and more frequent with abciximab, which is antibody derived and therefore has more antigenicity than a small peptide compound such as tirofiban. This hypothesis is supported by the fact that previous treatment with abciximab (but not tirofiban) was associated with an increased incidence of thrombocytopenia.

### Readministration of GP IIb/IIIa Antagonists

Recent data from the Reopro Readministration Registry6 show that the overall rates of thrombocytopenia after readministration were similar to those seen after first-time exposure, except that profound thrombocytopenia was more frequent after readministration. However, this finding was based on 23 patients who developed thrombocytopenia out of 500, whereas in our larger population, the readministration of abciximab was associated with the highest risk of developing thrombocytopenia even at multivariate analysis, thus confirming previous observations.7 This is even more important because the overall incidence of thrombocytopenia in our study was lower than in other studies of acute coronary
of care in patients undergoing PCI) was not associated with that pretreatment with thienopiridine (currently the standard of care in patients undergoing PCI) was not associated with an increased risk of thrombocytopenia.9

Thrombocytopenia and Outcome
Thrombocytopenia was associated with a worse outcome, with increased 30-day rates of bleeding, recurrent ischemia, urgent revascularization, and death. Among the group of patients who developed thrombocytopenia, the use of abciximab did not lead to a lower incidence of events, although there was a trend toward fewer periprocedural myocardial infarctions, which is consistent with the results of the main trial. The finding that thrombocytopenia is associated per se with a worse prognosis is in line with results of previous studies of patients not undergoing interventional procedures.10–13 This consistency indicates that the development of thrombocytopenia may identify patients at high risk for recurrent events even after coronary stenting and treatment with GP IIb/IIIa inhibitors. The close association between thrombocytopenia and the risk of nonhemorrhagic adverse outcomes remains unexplained. Platelets play a central role in the pathogenesis of acute coronary syndromes, and it is possible that platelet consumption leads to their activation, which could exacerbate coronary ischemia. This hypothesis is supported by the demonstrated association between the development of thrombocytopenia and death and nonfatal ischemic outcomes. Additional mechanisms for this association might be the temporary withholding of other antiplatelet agents such as aspirin or clopidogrel and the prothrombotic effects of platelet and red cell transfusions.

Study Limitations
All patients received heparin, and we cannot exclude the possibility that they may have developed heparin-induced thrombocytopenia. However, heparin was administered only for a short time because the protocol required its discontinuation at the end of the procedure. No per-procedure tests were specified to differentiate heparin-induced thrombocytopenia from GP IIb/IIIa–induced thrombocytopenia. However, the former generally occurs between 5 and 15 days after heparin administration, whereas thrombocytopenia developed during the first few hours after treatment in most of our patients and within 48 hours of study drug initiation in all patients.

Practical Implications
In conclusion, thrombocytopenia is observed more frequently in patients treated with abciximab. Close monitoring with blood sampling during the first few hours of treatment is therefore mandatory, and if thrombocytopenia is detected and confirmed, the GP IIb/IIIa antagonist should be promptly discontinued. Discontinuation of other antiplatelet agents or platelet transfusion in patients who have undergone stent implantation needs to be weighed against the increased risk of stent thrombosis and should be avoided except in cases of severe bleeding. Although the thrombocytopenia induced by GP IIb/IIIa inhibitors is self-limiting, it has an independent prognostic impact insofar as it is associated with a higher risk of death, ischemic events, and bleeding. Regardless of the cause, patients who develop thrombocytopenia should be carefully followed up during the first month because they are at high risk of recurrent ischemic events and death.

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References