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Occurrence and Clinical Significance of Pseudothrombocytopenia During Abciximab Therapy

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OBJECTIVES This study determined the incidence of pseudothrombocytopenia during abciximab therapy administered for percutaneous coronary interventions and compared the clinical course of patients with pseudothrombocytopenia with the clinical courses of patients with thrombocytopenia and patients with normal platelet counts.

BACKGROUND Although pseudothrombocytopenia has been previously reported during therapy with abciximab, the incidence and significance of this occurrence are unknown. The failure to differentiate pseudothrombocytopenia from thrombocytopenia could lead to unnecessary interruption of abciximab infusions or to platelet transfusions.

METHODS The incidences of pseudothrombocytopenia and thrombocytopenia were determined in four large placebo-controlled abciximab trials: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome of c7E3 GpIIb/IIIa Receptor Blockade (EPILOG) and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT). The clinical features, bleeding complications and major clinical outcomes of patients with pseudothrombocytopenia and those with thrombocytopenia were compared with each other and with those of patients with normal platelet count.

RESULTS Pseudothrombocytopenia occurred in 2.1% (95% confidence intervals [CI]: 1.7%, 2.5%) of abciximab-treated patients and in 0.6% of placebo-treated patients ($p < 0.001$). Thrombocytopenia occurred in 3.7% (95% CI: 3.2%, 4.2%) of abciximab-treated patients and in 1.8% (95% CI: 1.3%, 2.3%) of placebo-treated patients ($p < 0.001$). Patients with thrombocytopenia had significantly higher rates of major bleeding, major decreases in hemoglobin and increased transfusion requirements of both blood and platelets compared with those without thrombocytopenia. By contrast, pseudothrombocytopenic patients did not differ from patients with normal platelet counts in any of the measures of blood loss or transfusion requirements. Thrombocytopenic patients, but not those with pseudothrombocytopenia, had increased rates of revascularization at 30 days and six months. As previously reported, there was also a higher rate of death and myocardial infarction in the thrombocytopenic patients.

CONCLUSIONS Pseudothrombocytopenia is the cause of more than one third (36.3%) of low platelet counts in patients undergoing coronary interventions who are treated with abciximab. This study demonstrates that pseudothrombocytopenia is a benign laboratory condition that does not increase bleeding, stroke, transfusion requirements or the need for repeat revascularization. It is important to recognize pseudothrombocytopenia so that the beneficial effects of abciximab are not lost by premature termination of therapy. (J Am Coll Cardiol 2000; 36:75–83) © 2000 by the American College of Cardiology

The role of inhibitors of the platelet fibrinogen receptor (Gp IIb/IIIa) in the management of acute coronary ischemic syndromes and percutaneous coronary interventions has been well established by several large randomized clinical trials (1–6). Abciximab, a human/mouse chimeric Fab fragment that binds to the beta3 subunit of the fibrinogen receptor (7) was the first agent to be approved for percutaneous interventions. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, abciximab bolus and infusion resulted in a 35% reduction in the primary composite end point of death, nonfatal myocardial infarction (MI) or unplanned revascularization (1). Despite this benefit, the rate of major hemorrhage was doubled in the bolus plus infusion treatment arm compared with the placebo-treated group in EPIC. The Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome of c7E3 GpIIb/IIIa Receptor Blockade (EPILOG) and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) stent trials subsequently demonstrated that the rate of major hemorrhage can be lowered to that of patients not receiving abciximab by using lower weight-adjusted doses of concomitant heparin therapy and by early removal of arterial sheaths (3,4).

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CAPTURE	= c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina trial
EDTA	= ethylene diamine tetra acetic acid
EPIC	= Evaluation of 7E3 for the Prevention of Ischemic Complications trial
EPILOG	= Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome of c7E3 Gp IIb/IIIa Receptor Blockade trial
EPISTENT	= Evaluation of Platelet IIb/IIIa Inhibitor for Stenting trial
LIBS	= ligand induced binding sites
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
PTCP	= pseudothrombocytopenia

Despite the overall low rate of bleeding, the development of thrombocytopenia during abciximab therapy is associated with an increased rate of hemorrhage (8). Although the nadir platelet count during abciximab-induced thrombocytopenia is typically about 75K (8), this complication occasionally results in acute profound thrombocytopenia (<20K), requiring cessation of abciximab infusion and platelet transfusions (9). Abciximab-induced pseudothrombocytopenia (PTCP) has also been previously reported in early clinical studies (10), but its incidence in the large-scale clinical trials that have defined the current role of abciximab in acute coronary ischemic syndromes is unknown. Although PTCP is generally considered to be an in vitro artifact that does not require therapy, its significance in the setting of abciximab therapy for percutaneous coronary interventions (PCIs) has not been previously studied. Accordingly, in this paper, we report on the frequency of occurrence of PTCP in four major abciximab trials and compare the clinical course of patients with PTCP to those with thrombocytopenia.

METHODS

Study populations. The occurrence of PTCP was evaluated in four randomized trials of abciximab, which have been previously described in detail (1–4). These trials were approved by the institutional review board of the participating institutions. The EPIC trial was a prospective, randomized double-blind trial of 2,099 high risk intervention patients who received either a bolus plus infusion of placebo, a bolus of abciximab and an infusion of placebo or a bolus and 12 h infusion of abciximab (1). For the purposes of this study, the abciximab bolus only arm and the bolus plus infusion groups were combined. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial randomized 1,265 patients with refractory unstable angina to an 18 to 24 h infusion of abciximab or placebo before planned percutaneous intervention. The abciximab or placebo infusion was continued for 1 h after the PCI (2). The EPILOG trial was a prospective, double-blinded study in which 2,792 patients undergoing urgent or elective PCI were randomized to receive abciximab with standard-dose weight-adjusted heparin, abciximab with low-dose weight-adjusted heparin or placebo with standard-dose weight-adjusted heparin (3). The EPISTENT trial was a study of 2,399 patients undergoing elective PCI who were randomly assigned to receive stenting plus placebo, stenting plus abciximab or balloon angioplasty plus abciximab (4).

Platelet counts. Blood samples for platelet counts were obtained at 30 min, 2, 12 and 24 h after study agent administration. Follow-up platelet counts were obtained at four days and at one, two and four weeks. If a platelet count of <100,000/Ul was obtained that also represented a decrease of at least 25% below baseline value, then additional platelet counts in EDTA, citrate and heparin anticoagulants were drawn. A smear from blood in each of these anticoagulants was requested. The presence of platelet aggregates on any sample obtained for platelet count was reported.

Definitions of thrombocytopenia and PTCP. The distinction between thrombocytopenia and PTCP was made for all trials by the same reviewer (D.C.S.), who was blinded to the treatment groups. Thrombocytopenia was defined by a platelet count $<100 \times 10^9$/liter and with a ≥25% decrease from the baseline count without evidence for PTCP. Pseudothrombocytopenia required one or more of the following: 1) a difference between the platelet count in two anticoagulants, with one having a count at least 20% lower than the count in the comparison anticoagulant. In this study, the anticoagulants that were compared were ethylene diamine tetra acetic acid (EDTA) and citrate in more than 90% of cases, 2) platelet clumping on a blood smear made from anticoagulated blood, 3) a normal platelet count on a blood smear made from nonanticoagulated blood or 4) an unexplained drop in platelet count at 30 min to 4 h after abciximab bolus with recovery to a normal count within 4 h after the nadir. This last criterion was developed when review of the first cases revealed that there was a frequent association between low platelet counts and one of the other three criteria for PTCP at this time point.

Statistical analyses. Logistic regression was performed on discrete outcomes of interest using indicator variables for: 1) PTCP, 2) thrombocytopenia, 3) neither and 4) treatment as independent variables. Interaction terms between treatment and thrombocytopenia, PTCP and neither were also tested to see if associations differed between treatment groups; if an interaction test was positive, the association of interest was examined separately in the abciximab and placebo groups. A linear model was used to test for associations between individual characteristic outcomes and treatment. Each characteristic was studied as a dependent variable. Independent variables were indicators for the status of thrombocytopenia, treatment and interactions. A chi-square test was used to compare the four study differences.

Study limitations. Our study has some limitations. Thrombocytopenia or PTCP may have occurred before or after outcome events. Thus, these analyses examined the association of PTCP and thrombocytopenia with other outcomes rather than any cause-effect relationship. The etiology of thrombocytopenia was not investigated rigorously in most cases. A potential interaction between heparin and the occurrence of thrombocytopenia and PTCP could not be defined.

RESULTS

Thrombocytopenia occurred in 205 of 5,476 abciximab-treated patients (3.7%) and in 56 of 3,079 placebo-treated patients (1.8%; $p < 0.001$, Fisher's exact test). Pseudothrombocytopenia occurred in 2.1% (117/5,476) of abciximab-treated patients and in 0.6% (17/3,079) of placebo-treated patients ($p < 0.001$, Fisher's exact test). The rates of PTCP in placebo-treated patients in the individual trials were 0.6% (CAPTURE), 1.3% (EPIC), 0.2% (EPILOG) and 0.2% (EPISTENT). The rates of PTCP in abciximab-treated patients in the individual trials were 4.0% (CAPTURE), 1.7% (EPIC), 1.9% (EPILOG) and 2.1% (EPISTENT). The frequency of premature termination of planned infusion was 6.5% (195/3,006) for the patients with normal platelet counts treated with placebo and 7.5% (384/5,154) for this group when treated with abciximab. Thrombocytopenic patients had a much higher rate of early cessation of the infusion with 44.6% (25/56) of the placebo-treated and 34.6% (71/205) of the abciximab-treated patients being affected. None (0/17) of the PTCP patients treated with placebo and 12.0% (14/117) of the PTCP patients treated with abciximab had early termination of therapy.

Table 1 shows the clinical characteristics of all patients from the four trials. As previously reported during abciximab therapy (8), patients with thrombocytopenia were older than those with normal platelet counts ($p = 0.0018$). There was a trend ($p = 0.09$) toward an association between older age and the occurrence of PTCP. Patients with PTCP in the placebo-treated group were more likely to have peripheral vascular disease and tended to be women. When all of the groups were combined, there were no significant differences in any of the demographic or clinical characteristics between the abciximab-treated and the placebo-treated patients (Table 1, last column on the right), suggesting that randomization successfully balanced these characteristics.

Tables 2–4 show the in-hospital bleeding and transfusion requirements in the three groups of patients. Table 2 includes all patients, Table 3 is for the group with coronary artery bypass grafting (CABG), and Table 4 is for patients who did not have CABG. Patients with thrombocytopenia had significantly higher rates of maximum bleeding, major decreases in hemoglobin, and increased transfusion requirements for both blood and platelets. Overall, 67.9% of

Table 1. Demographic Characteristics of Patients With Pseudothrombocytopenia, Thrombocytopenia and Neither

	Neither		Pseudothrombocytopenia				Thrombocytopenia				
	Placebo (n = 3,006)	Abciximab (n = 5,154)	Placebo (n = 17)	Abciximab (n = 117)	Overall	p Value Interact	Placebo (n = 56)	Abcix (n = 205)	Overall	p Value Interact	p Val versus placebo
Age yr	60 (52,68)	60 (52,68)	67 (58,69)	63 (53,70)	0.0919	0.3998	64 (55,72)	62 (55,70)	0.0018	0.2726	0.1883
Gender, M, %	73.0	73.1	52.9	72.6	0.0724	0.1089	69.6	72.7	0.5772	0.6750	0.1100
Weight, kg	82 (72,93)	82 (73,93)	76 (73,83)	81 (74,94)	0.1419	0.1136	82 (73,90)	79 (70,90)	0.2503	0.7606	0.1847
Race, %											
Caucasian	91.8	91.5	100.0	89.7	0.9578	0.9570	96.4	89.8	0.2246	0.1540	0.9528
African-American	4.2	4.8	0.0	4.3	0.9532	0.9538	1.8	6.8	0.3861	0.2366	0.9472
Other	3.9	3.5	0.0	5.1	0.9577	0.9561	1.8	2.9	0.4346	0.5859	0.9540
Unknown	0.1	0.1	0.0	0.9	0.9778	0.9722	0.0	0.5	0.9597	0.9527	0.9528
Diabetes, %	21.2	21.2	23.5	19.7	0.8142	0.7091	32.1	17.6	0.0505	0.0200†	0.1450
Hypertension, %	52.9	53.9	52.9	49.6	0.9969	0.7370	64.3	52.7	0.0934	0.0987	0.2809
Smoking, %	35.5	34.9	35.3	25.6	0.9839	0.4329	28.6	27.8	0.2827	0.9711	0.4657
Prior CVA, %	1.8	2.0	0.0	2.6	0.9550	0.9537	1.8	1.0	0.9952	0.5625	0.9568
PVD	7.7	7.8	23.5	6.8	0.0227	0.0340*	7.1	9.3	0.8872	0.6462	0.1905
Prior PCI	20.1	19.8	35.3	19.7	0.1286	0.1638	12.5	16.6	0.1644	0.4349	0.5292
Prior CABG	10.9	10.3	11.8	12.8	0.9105	0.8404	7.1	14.6	0.3730	0.1223	0.3246
CHF	5.6	6.1	5.9	5.1	0.9581	0.8345	7.1	7.8	0.6178	0.9897	0.9130

Data given as median (25^{th}, 75^{th} percentiles). CABG = coronary artery bypass grafting; CHF = congestive heart failure; CVA = cerebrovascular accident (stroke); PCI = percutaneous intervention; PVD = peripheral vascular disease.
*The rate of PVD is associated with pseudothrombocytopenia among placebo patients (p value = 0.0227) but not abciximab patients (p value = 0.7065); †There is no significant association between thrombocytopenia and diabetes, either in the placebo group (p value = 0.0505) or in the abciximab group (p value = 0.2081).

Table 2. Bleeding, Hematological and Transfusion Parameters in All Patients

	Neither		Pseudothrombocytopenia				Thrombocytopenia				
Clinical Outcome	Placebo (n = 3,006)	Abciximab (n = 5,154)	Placebo (n = 17)	Abciximab (n = 117)	p Value vs. Neither	p Value Interact	Placebo (n = 56)	Abciximab (n = 205)	p val vs. Neither	p Value Interact	p val-vs. Placebo
Mj bld, %	2.6	4.4	0.0	1.7	0.9507	0.9559	66.1	25.9	<0.001	<0.001*	0.9651
Mj dec in Hgb	1.3 (2.1,0.6)	1.4 (2.3,0.7)	1.6 (2.0,1.1)	1.7 (2.4,0.9)	0.7227	0.7443	7.1 (10.7,3.0)	2.3 (5.0,1.4)	<0.001	0.001†	<0.001
Blood	3.2	5.4	5.9	4.3			67.9	26.3			
No. U											
1–2, %	2.1	3.3	5.9	2.6	0.3022	0.2697	16.1	6.8	<0.001	0.0033#	0.0748
3–5, %	0.8	1.6	0.0	1.7	0.9685	0.9682	16.1	9.3	<0.001	0.008§	0.9705
>5, %	0.3	0.5	0.0	0.0	0.9633	0.9968	35.7	10.2	<0.001	<0.001‖	0.9890
Max dec in plt	12.0 (18.7,6.2)	13.4 (23.2,5.7)	18.3 (37.5,8.0)	51.9 (65.8,28.5)	<0.001	<0.001#	57.9 (76.4,29.3)	61.4 (76.8,45.1)	<0.001	0.0906	<0.001
Plt trns %	0.4	1.3	0.0	2.6	0.9662	0.9631	35.7	25.9	<0.001	<0.001¶	0.9651

Data given as median (25^{th}, 75^{th} percentiles). Mjr bld = major Bleeding; Mj dec in Hgb = major decrease in Hemoglobin; Blood = PRBC or whole Blood; Mx dec in plt = maximum decrease in platelets; Plt trns = platelet transfusions.
*There is a significant association between thrombocytopenia and major bleeding, among placebo and abciximab patients (p value < 0.001); †There is significant association between thrombocytopenia and major decrease in hemoglobin, among placebo and abciximab patients (p value < 0.001); ‡There is significant association between thrombocytopenia and 1–2 U of blood transfusion among placebo patients (p value < 0.001) and abciximab patients (p value = 0.0069); §There is significant association between thrombocytopenia and 3–5 U of blood transfusion among placebo and abciximab patients (p value < 0.001; ‖There is significant association between thrombocytopenia and >5 U of blood transfusion among placebo and abciximab patients (p value < 0.001); ¶There is significant association between thrombocytopenia and platelet transfusion among placebo and abciximab patients (p value < 0.001); #There is significant association between pseudothrombocytopenia and maximum decrease in platelets among placebo and abciximab patients (p value < 0.001).

Table 3. Bleeding, Hematological and Transfusion Parameters in CABG Patients

	Neither		Pseudothrombocytopenia				Thrombocytopenia				
Clinical Outcome	Placebo (n = 3,006)	Abciximab (n = 5,154)	Placebo (n = 17)	Abciximab (n = 117)	p Value vs. Neither	p Value Interact	Placebo (n = 56)	Abciximab (n = 205)	p Value vs. Neither	p Value Interact	p Value vs. Placebo
CABG, n	74	94	0	2			34	35			
Mj bld, %	48.6	66.0	0.0	50.0	0.6439	NA	88.2	85.7	<0.001	0.2325	0.7562
Mx dec in Hgb	4.8 (7.3,1.8)	6.4 (7.8,3.8)	NA	2.0 (3.2,0.7)	0.1792	NA	9.0 (10.8,6.0)	9.3 (14.0,6.5)	<0.001	0.8686	0.1073
Blood	40.5	62.8	NA	50.0			88.2	85.7			
No. U											
1–2, %	23.0	17.0	NA	0.0	0.9908	NA	23.5	14.3	0.9492	0.7471	0.3304
3–5, %	12.2	28.7	NA	50.0	0.5258	NA	20.6	25.7	0.2571	0.2742	0.6146
>5, %	5.4	14.9	NA	0.0	0.9907	NA	44.1	45.7	<0.001	0.1671	0.8940
Max dec in plt	28.9 (48.5,10.4)	30.7 (42.9,12.8)	NA	70.7 (53.4,88.0)	0.0056	NA	66.2 (79.0,55.3)	64.3 (71.1,46.7)	<0.001	0.3301	0.2347
Plt trns %	17.6	41.5	0.0	50.0	0.8100	NA	52.9	65.7	<0.001	0.2788	0.2816

Data given as median (25^{th}, 75^{th} percentiles).
CABG = coronary artery bypass grafting; Mjr bld = major bleeding; Mx dec in Hgb = maximum decrease in hemoglobin blood = PRBC or whole blood; Mx dec in plt = maximum decrease in platelets; Plt trns = platelet transfusions. The maximum decrease in the hemoglobin was adjusted for transfusion. If the maximum change was an increase, that value was set to 0.

Table 4. Bleeding, Hematological and Transfusion Parameters in Non-CABG Patients

Clinical Outcome	Neither		Pseud			Thrombo				
	Placebo (n = 2,932)	Abcix (n = 5,060)	Placebo (n = 17)	Abcix (n = 115)	p Value vs. Neither	p Value Interact	Placebo (n = 22)	Abcix (n = 170)	p Value vs. Neither	p Value Interact	p Value vs. Placebo
Mj bld, %	1.4	3.2	0.0	0.9	0.9653	0.9703	31.8	13.5	<0.001	<0.001*	0.9743
Mx dec in Hgb	1.3 (2.0,0.6)	1.4 (2.3,0.7)	1.6 (2.0,1.1)	1.7 (2.4,0.9)	0.5053	0.6821	2.7 (9.2,1.7)	1.9 (3.2,1.1)	<0.001	<0.001†	<0.001
Blood	2.2	4.3	5.9	3.5			36.4	14.1			
No. U											
1–2, %	1.6	3.0	5.9	2.6	0.1895	0.2068	4.5	5.3	0.2900	0.6447	0.4019
3–5, %	0.5	1.1	0.0	0.9	0.9635	0.9645	9.1	5.9	<0.001	0.1598	0.9666
>5, %	0.1	0.2	0.0	0.0	0.9718	0.9978	22.7	2.9	<0.001	0.0016‡	0.9889
Mx dec in plt	11.9 (18.4,6.2)	13.3 (22.9,5.7)	18.3 (37.5,8.0)	51.8 (65.5,28.5)	<0.001	<0.001§	32.9 (53.7,22.2)	60.9 (78.5,45.0)	<0.001	<0.001§	<0.001
Plt trns %	0.0	0.5	0.0	1.7	1.000	0.9942	9.1	17.6	0.3931	0.5750	0.9906

Data given as median (25^{th}, 75^{th} percentiles).
Blood = PRBC or whole blood; Mjr bld = major bleeding; Mx dec in Hgb = maximum decrease in hemoglobin; Mx dec in plt = maximum decrease in platelets; Plt trns = platelet transfusions.
The maximum decrease in the hemoglobin was adjusted for transfusion. If the maximum change was an increase, that value was set to 0.
*The rate of major bleed is associated with thrombocytopenia among placebo and abciximab patients (p value < 0.001); †there is a significant association between thrombocytopenia and major decrease in hemoglobin in both the placebo and abciximab groups (p value < 0.001); ‡the rate of >5 units PRBC or whole blood is associated with thrombocytopenia among placebo and abciximab patients (p value < 0.001); §there is a significant association between thrombocytopenia and maximum decrease in platelet in both the placebo and abciximab groups (p value < 0.001); ‖there is also a significant association between pseudothrombocytopenia and maximum decrease in platelet in both the placebo and abciximab groups (p value < 0.001).

patients with thrombocytopenia in the placebo-treated group and 26.3% of patients with abciximab-induced thrombocytopenia received blood transfusions. By contrast, the proportions of patients receiving blood and platelet transfusions in the PTCP group were similar to those in the group of patients without lowered platelet counts. The decrease in platelet count was the only significant hematological difference between the PTCP and the "neither" groups. When all three groups were combined, the patients treated with abciximab were more likely to have a major decrease in hemoglobin and had a larger maximum decrease in the platelet count. There was a trend ($p = 0.075$) toward increased transfusion of 1 to 2 U of blood in abciximab-treated patients compared with those who received placebo. However, there were also important differences in bleeding depending on the heparin strategy, with no elevated bleeding noted with reduced heparin regimens (3,4).

The 30-day clinical outcomes of death, MI and stroke are shown in Table 5. There was a higher rate of death in the thrombocytopenic group ($p < 0.001$) compared with the "neither" group. There was a trend toward increased death in the placebo-treated PTCP group ($p = 0.051$). There was a higher rate of MI in the placebo-treated thrombocytopenic group compared with the "neither" group. When thrombocytopenic, PTCP and "neither" groups were combined, the patients treated with abciximab had lower rates of MI ($p = 0.0069$) compared with those treated with placebo. The frequency of stroke was very low in all groups and was not increased by thrombocytopenia or PTCP. Patients with thrombocytopenia, especially those who received placebo, had significantly increased rates of revascularization with PCI and CABG at 30 days.

At six months (Table 6), the higher rate of death in the thrombocytopenia group versus the "neither" group persisted ($p < 0.001$). There was also a higher rate of MI and repeat revascularization with CABG (but not PCI) in the thrombocytopenia group compared with the neither group. When all three groups were combined, the patients treated with abciximab had lower rates of MI and need for repeat revascularization compared with those treated with placebo.

At 30 days and at six months, there was no increase in death, MI, stroke or need for repeat revascularization in the PTCP group compared with the "neither" group.

DISCUSSION

In the four studies that were reviewed for this report, PTCP occurred in 2.1% (117/5,476) of abciximab-treated patients and in 0.6% (17/3,079) of placebo-treated patients ($p < 0.001$). Pseudothrombocytopenia was judged to be the etiology of 32.2% of all cases of low platelet counts in the overall study populations (placebo- and abciximab-treated) and 36.3% of all cases in the abciximab-treated group. Thus, it is important to recognize PTCP, a condition that does

Table 5. 30-Day Clinical Outcomes

Clinical Outcome	Neither		Pseudothrombocytopenia				Thrombocytopenia				
	Placebo (n = 3,006)	Abcix (n = 5,154)	Placebo (n = 17)	Abcix (n = 117)	p Value vs. Neither	p Value Interact	Placebo (n = 56)	Abcix (n = 205)	p Val vs. Neither	p Value Interact	p Value vs. Placebo
Death %	0.8	0.6	5.9	0.0	0.0511	0.9433	12.5	5.9	<0.001	0.3693	0.9394
MI %	8.0	4.3	11.8	3.4	0.5657	0.4604	51.8	13.2	<0.001	<0.001*	0.0069
Stroke %	0.3	0.3	0.0	0.0	0.9739	0.9993	0.0	0.5	0.9526	0.9503	0.9772
Hem %	0.1	0.1	0.0	0.0	0.9845	0.9997	0.0	0.0	0.9718	0.9995	0.9998
Nonhem %	0.2	0.2	0.0	0.0	0.9785	0.9991	0.0	0.5	0.9611	0.9574	0.9805
Re Rev %§	7.5	5.5	5.9	3.4	0.8063	0.8387	60.7	22.4	<0.001	<0.001†	0.1105
Re PCI %	5.2	3.7	5.9	1.7	0.9031	0.4594	14.3	6.8	0.0046	0.3285	0.1922
CABG %	2.5	1.8	0.0	1.7	0.9558	0.9561	60.7	17.1	<0.001	<0.001‡	0.9656

*There is a significant association between thrombocytopenia and MI in both the placebo and abciximab group (p value < 0.001); †there is a significant association between thrombocytopenia and repeat revascularization, in both the placebo and abciximab group (p value < 0.001); ‡there is a significant association between thrombocytopenia and CABG, in both the placebo and abciximab group (p value < 0.001); §analysis of revascularization excludes patients with staged PCI.

CABG = coronary artery bypass grafting; MI = myocardial infarction; Hem = hemorrhagic stroke; Nonhem = non hemorrhagic stroke; Re Rev = repeat revascularization; Re PCI = repeat PCI.

Table 6. Six-Month Clinical Outcomes

Clinical Outcome	Neither		Pseudothrombocytopenia				Thrombocytopenia				
	Placebo (n = 3,006)	Abcix (n = 5,154)	Placebo (n = 17)	Abcix (n = 117)	p Value vs. Neither	p Value Interact	Placebo (n = 56)	Abcix (n = 205)	p Value vs. Neither	p Value Interact	p Value vs. Placebo
Death	1.7	1.6	5.9	0.0	0.2232	0.9527	17.9	8.3	<0.001	0.0950	0.9494
MI	9.1	5.7	17.6	3.4	0.2350	0.1129	53.6	16.1	<0.001	<0.001*	0.0005
Re Rev%*	19.8	18.8	29.4	20.5	0.3269	0.4784	66.1	33.2	<0.001	0.001†	0.0073
Re PCI%*	14.9	14.2	23.5	15.4	0.3263	0.4559	19.6	14.1	0.327	0.3944	0.2440
CABG%	6.3	5.6	11.8	6.0	0.3640	0.4636	60.7	21.5	<0.001	<0.001‡	0.0097

*There is a significant association between thrombocytopenia and MI, among placebo and abciximab patients (p Value < 0.001); †there is a significant association between thrombocytopenia and repeat revascularization among placebo and abciximab patients (p value < 0.001); ‡there is a significant association between thrombocytopenia and CABG, among placebo and abciximab patients (p value < 0.001).

CABG = coronary artery bypass grafting; Re Rev = repeat revascularization; Re PCI = repeat PCI.

not require specific therapy or the premature cessation of abciximab from thrombocytopenia, a condition that may mandate an intervention.

Christopoulos and Machin (10) first reported the occurrence of PTCP in 19% of 21 patients participating in early clinical studies of Gp IIb/IIIa inhibition in which chimeric whole molecule 7E3 IgG or the c7E3 Fab fragment was infused for up to 96 h (10). The higher percentage of PTCP in their study compared with the current report probably reflects the small sample size. Other factors that could account for this difference include the molecular form of abciximab that was used or the long duration of therapy. The higher PTCP rate in the CAPTURE trial (4%) in which an 18 to 26 h infusion was used compared with the other studies (1.7 to 2.1%) in which a 12 h infusion or bolus only was used emphasizes the importance of the treatment regimen. The patients reported in these four studies were treated for the first time with abciximab. Although a preliminary study (11) suggests that the incidence of thrombocytopenia is slightly increased (to 4.6%) with repeat dosing, further analyses of the effects of readministration on both thrombocytopenia and PTCP are warranted and are ongoing.

Prior studies of PTCP. Previous reports have documented the occurrence of PTCP in up to 0.2% of the healthy population and in 1.9% of hospitalized patients (12–14). Although PTCP is an infrequent condition, it accounts for a sizable fraction (7.5 to 15.3%) of all cases of "thrombocytopenia" that are referred to hematologists for further evaluation (15). The phenomenon of PTCP that occurs in the absence of abciximab therapy is due to platelet autoantibodies that recognize usually cryptic platelet antigens that are exposed in vitro. The presence of certain anticoagulants (especially EDTA), low temperatures and prolonged time intervals between blood draws and assays are factors that enhance the occurrence of PTCP (16–19). The autoantibodies are usually IgG or IgM with the most commonly reported antigenic target being platelet glycoprotein IIb (16) although other antigens including phospholipids have been described (18). Ethylene diamine tetra acetic acid is the most commonly reported anticoagulant to induce PTCP. The calcium chelating activity of EDTA is thought to remove calcium from binding sites within Gp IIb or Gp IIIa, resulting in exposure or conformational alteration of the molecule(s), thereby allowing the previously cryptic antigen to interact with the autoantibody (17). As a result of the frequent association with EDTA anticoagulant a commonly recommended method to screen for this phenomenon and the method most commonly used in the studies in this report is to obtain simultaneous platelet counts in EDTA and sodium citrate anticoagulants. However, the term "EDTA-dependent PTCP" has been rejected by some investigators, since PTCP has been observed in citrate anticoagulants and even in nonchelating anticoagulants such as hirudin and D-phenylalanine-proline-arginine-chloromethyl ketone (19). Bizzaro et al. (17) noted that in 15 of their 93 cases (10.8%) with PTCP and antiplatelet antibodies, agglutination occurred in citrate at room temperature (17). In this study, 14 of the 117 cases of PTCP that occurred during abciximab therapy were documented to occur in the presence of citrate anticoagulant.

Since the autoantibodies that induce PTCP often are most active in a time-dependent fashion at 4 to 20° C, it has been suggested that the most reliable way to obtain accurate platelet counts is to perform platelet counts on blood at 37° C (17). However, even this method will cause a few cases to be mislabeled since approximately 17% of autoantibodies are reactive at 37°C in the presence of anticoagulants (17). The autoantibodies that are reactive at 37°C and in citrate are more likely to be of the IgM class (17). The gold standard for differentiating PTCP from thrombocytopenia may, therefore, be to perform a platelet count on nonanticoagulated blood obtained by finger stick, in which case a normal platelet count should be obtained. In contrast, a blood smear prepared from EDTA-anticoagulated blood typically reveals platelet clumping.

The source of the autoantibodies that are thought to cause PTCP is unknown. Sakurai et al. (20) reported that a group of patients who developed PTCP during hospitalization had been treated with antibiotics 4 to 10 days before the onset of this condition. They hypothesized that the autoantibodies first arose to antibiotics then cross-reacted to platelet membranes. They demonstrated that presupplementation of EDTA tubes with aminoglycosides prevented PTCP and that aminoglycosides added after the onset of platelet clumping could dissociate the aggregates (20). However, there was no apparent correlation between the antibiotic that the patient had taken therapeutically and the antibiotic that was most effective in inhibiting platelet clumping, casting doubt on the theory that antiplatelet antibodies arise from cross-reacting antibodies to these drugs. Another theory for the origin of the autoantibodies directed to platelets is that they are involved in removing senescent circulating platelets (17).

Potential mechanisms for abciximab-induced PTCP. The etiology of the increased prevalence of PTCP in abciximab-treated patients is also obscure. Christopoulos and Machin (10) performed flow cytometric analysis of platelet surface IgG in platelets from two patients with abciximab-induced PTCP and demonstrated a time- and room temperature-dependent increase in surface IgG, which was not present on EDTA samples taken before the infusion of c7E3 or in citrate anticoagulated samples taken during the infusion (10). Among 19 patients receiving c7E3-Fab, the one with the most severe PTCP also had the most surface IgG (10). This finding led Christopoulos and Machin to propose that there might be naturally occurring anti-Fab antibodies and that these might bridge platelets to

form agglutination. Another possibility is that the binding of the Fab fragment to the beta3 component of the fibrinogen receptor could alter the conformation of the molecule and, in concert with the anticoagulant-induced changes, enhance access of autoantibodies to Gp IIb or other platelet antigens. Abciximab is known to induce the expression of conformational changes in the fibrinogen receptor, as detected by the expression of novel antigens (ligand induced binding sites [LIBS]) (21,22). The potential for abciximab-induced conformational changes in the fibrinogen receptor and the ability of some platelet autoantibodies to react at 37° C also raises the possibility that the mechanisms for PTCP and thrombocytopenia during abciximab therapy could be related. Thus, it is possible that abciximab alone, in the absence of anticoagulants, is adequate to expose the cryptic epitope for warm-reacting platelet autoantibodies, leading to the immune-mediated clearance of platelets and thrombocytopenia. This hypothesis is consistent with the observation that the induction of LIBS epitopes on platelets after abciximab therapy is inversely correlated with the platelet count (21). This possibility is also attractive because of the relative high frequency of PTCP as a cause of low platelet counts with abciximab therapy and by the fact that the mechanism for abciximab-induced thrombocytopenia remains unknown.

Clinical implications of abciximab-induced thrombocytopenia and PTCP. Despite the possibility that the mechanisms for PTCP and thrombocytopenia are related, it is clear that the clinical courses of the entities are distinct. Patients with thrombocytopenia had a higher rate of death and MI than those with PTCP and those with neither condition. Furthermore, patients with thrombocytopenia, but not PTCP, had much higher rates of bleeding and transfusion requirements. The onset of thrombocytopenia, especially when severe, results in the cessation of abciximab infusion and may prompt platelet transfusions. These actions, while appropriate in the case of profound thrombocytopenia (9), should be considered cautiously when the platelet decrement is less severe, for two reasons. First, abciximab-treated thrombocytopenic patients had better outcomes than did those who developed thrombocytopenia on placebo. Abciximab reduced the rates of death, MI and revascularization without increased bleeding, despite the occurrence of thrombocytopenia. Indeed, the thrombocytopenic group appeared to accrue the greatest benefit from abciximab therapy. The second caveat is that the development of a low platelet count during abciximab therapy represented PTCP in slightly more than one-third (36.3%) of patients.

Cessation of the abciximab infusion or platelet transfusion could lead to an unnecessary abrogation of the beneficial effects of abciximab therapy. The rate of premature termination of therapy was much higher for thrombocytopenic patients (44.6%) than for PTCP patients (12%), probably because thrombocytopenic patients had a higher rate of bleeding or because clinicians accurately made the diagnosis of PTCP in most cases and elected to continue therapy. It is important that the distinction between PTCP and thrombocytopenia be made so that the full benefits of abciximab will be obtained.

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