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Achieved Platelet Aggregation Inhibition After Different Antiplatelet Regimens During Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

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OBJECTIVES To evaluate the extent of platelet aggregation inhibition in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI), treated with different antiplatelet agents and dosages.

BACKGROUND The extent of platelet aggregation inhibition is an independent predictor of major cardiac events after elective PCI. In STEMI patients undergoing PCI, routine dose of antiplatelet agents may be associated with less effective platelet aggregation inhibition.

METHODS Patients were treated with clopidogrel before angiography and randomized to abciximab, tirofiban, high-dose tirofiban, or no glycoprotein (GP) IIb/IIIa inhibitor; GP IIb/IIIa inhibitor bolus, followed by maintenance infusion, was administered after angiography, but before PCI. Platelet aggregation inhibition was assessed before angiography, immediately after PCI, and 1 and 6 h afterwards.

RESULTS The total study population consisted of 112 patients. Platelet aggregation inhibition was variable for individuals and suboptimal for all agents, particularly in the periprocedural period. Only with high-dose tirofiban, mean periprocedural platelet aggregation inhibition exceeded 80%. Angiographic parameters after PCI were not different between the groups. No relationship was found between the level of platelet aggregation and parameters of PCI success (Thrombolysis In Myocardial Infarction frame count and myocardial blush grade), after combining the data from all four groups studied.

CONCLUSIONS Platelet aggregation inhibition in STEMI patients undergoing PCI, treated with antiplatelet agents, is variable and suboptimal for all agents and dosages studied. Only with high-dose tirofiban, mean periprocedural platelet aggregation inhibition exceeded 80%. However, no relationship of platelet aggregation inhibition and angiographic outcome was found in this patient cohort. (J Am Coll Cardiol 2004;44:1187–93) © 2004 by the American College of Cardiology Foundation

The extent of pharmacologically induced platelet aggregation inhibition is an independent predictor of major cardiac events after percutaneous coronary intervention (PCI) (1,2). The extent of platelet aggregation inhibition depends on clinical presentation and type and dosage of antiplatelet agents (3–6). Patients with an acute coronary syndrome may have decreased response to antiplatelet agents (3,4), and tirofiban may be less effective than abciximab within 60 min after administration (5). Improving platelet aggregation inhibition by increasing the bolus dose of the glycoprotein (GP) IIb/IIIa inhibitors has been described in patients undergoing elective or high-risk PCI and in patients with non–ST-segment elevation myocardial infarction (7–10). This was not associated with an increased risk of major bleeding (11,12). In patients with ST-segment elevation myocardial infarction (STEMI), routine dose of antiplatelet agents may be associated with less effective platelet aggregation inhibition.

We evaluated the extent of platelet aggregation inhibition in patients with STEMI undergoing PCI, treated with different antiplatelet agents and dosages.

METHODS

Patient selection. Patients with STEMI who were candidates for PCI within six h after onset of symptoms were included. Patients over 80 years of age, as well as women <50 years of age, patients who were treated with thrombolytic therapy or GP IIb/IIIa inhibitors within the prior 24 h, or patients on warfarin or acenocoumarol within the last 7

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Abbreviations and Acronyms
GP = glycoprotein
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

days were excluded. Patients with a contraindication to GP IIb/IIIa inhibitors, severe heart failure or cardiogenic shock (Killip class III or IV), and patients who were on hemodialysis were also excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki and with the laws and regulations applicable in the Netherlands. The local institutional review board approved the protocol. As patients were enrolled in an emergency situation, before participation in the study (i.e., administration of study medication), oral informed consent was obtained in all patients by a physician in the emergency room in the presence of an independent witness (nurse), who signed as a confirmation. Written informed consent was requested after the PCI.

Study protocol. The study was conducted as an open-label, observational, randomized, single-center study. It was designed to compare the extent of platelet aggregation inhibition in patients with STEMI who were treated with PCI within 6 h after onset of symptoms and who were treated with different antiplatelet agents. All patients were treated with 300 mg of clopidogrel orally before angiography. Patients were then randomized to treatment with abciximab, tirofiban, high-dose tirofiban, or no GP IIb/IIIa inhibitor ("control group"). In case the patient was allocated to therapy with GP IIb/IIIa inhibitors, the GP IIb/IIIa inhibitor bolus, immediately followed by the maintenance infusion, was administered after acute angiography, but before PCI. The study design is depicted in Figure 1. Computerized randomization was performed in our emergency room. All patients received a bolus of 5,000 IU of unfractionated heparin intravenously together with 500 mg of aspirin intravenously before the PCI. After the procedure, all patients were treated with 100 mg of aspirin daily. Clopidogrel was continued for one month in a dose of 75 mg orally. Abciximab was administered as a bolus of 0.25 mg/kg intravenously followed by a maintenance infusion of 0.125 μg/kg/min (max 10 μg/min) and continued for 12 h after the procedure. Normal dose tirofiban consisted of a bolus of 10 μg/kg intravenously, followed by a maintenance infusion of 0.15 μg/kg/min, and this was continued for 12 h after the PCI. In the patients who received high-dose tirofiban, a bolus of 25 μg/kg was given. The maintenance

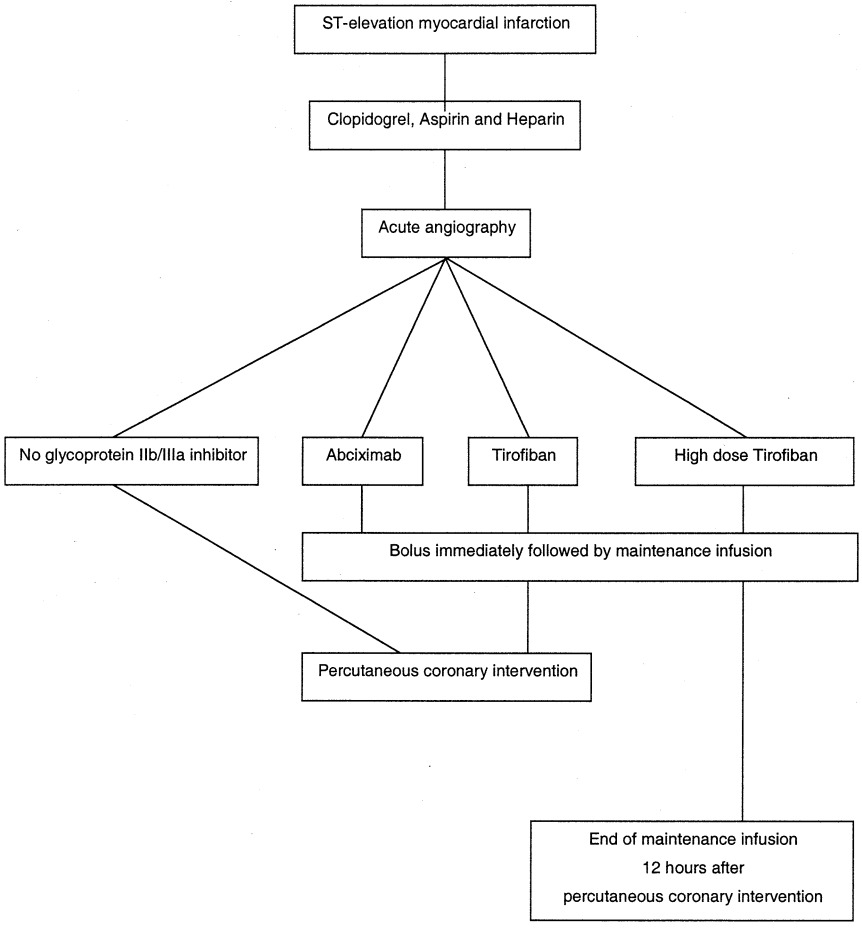

Figure 1. Design of the study.

infusion of 0.15 μg/kg/min was the same as in the normal dose group. Coronary angiography was performed according to standard procedure as soon as possible after admission, followed by PCI of the infarct-related vessel.

Assessment of inhibition of platelet aggregation. Blood samples to assess the extent of platelet aggregation inhibition were taken at four different time points: 1) after admission but before acute coronary angiography (baseline); 2) immediately after PCI; 3) 1 h after PCI; and 4) 6 h after PCI.

Platelet aggregation inhibition was assessed on a routine blood cell counter in the local laboratory of clinical chemistry with ethylenediamine tetraacetic acid as anticoagulant, using 20 μM/l adenosine diphosphate as agonist (Sysmex K 4500, Sysmex Corp., Kobe, Japan). The following procedure was performed: a reference platelet count was performed on 1 ml of fresh whole blood in a tube containing ethylenediamine tetraacetic acid as the anticoagulant. The sample was then passed through the cell counter, and the platelet count was determined. This process was repeated with a second sample of 1 ml of fresh whole blood in a tube containing both PPACK and 20 μM/l ADP. In the presence of ADP, platelets associate and aggregate. As the aggregated platelets exceed the threshold limitations for platelet size, they are no longer counted as individual platelets. The ratio of the platelet count between the agonist and reference tubes was calculated as percent platelet aggregation. Therefore, platelet aggregation inhibition could be calculated by taking 100 (%) minus percent platelet aggregation (%). In our laboratory (K.M., R.J.S.), we showed a correlation coefficient of 0.90 between the Sysmex K 4500 and the ICHOR point-of-care platelet analyzer (Helena Laboratories, Beaumont, Texas) (13,14) to validate the Sysmex K 4500 platelet aggregation measurement.

Definitions. In-hospital reinfarction and mortality rates were assessed during hospital stay. Recurrent myocardial infarction was defined as a new increase in creatinine kinase-MB fraction of more than 3× the upper limit of normal, whether or not accompanied by chest pain and/or electrocardiographic changes and present in two separate blood samples. Bleeding complications were closely monitored clinically and by serial determinations of hemoglobin. Prolonged bleeding at the catheter insertion site, hematomas, or signs of any other blood loss were critically evaluated. Major bleeding was defined as a fall in hemoglobin of ≥2.0 mmol/l and the need for transfusion of ≥2 U of blood, corrective surgery or both, or as bleeding that resulted in documented intracranial or retroperitoneal hemorrhage. Minor bleeding was defined as a fall in hemoglobin of ≥2.0 mmol/l without the need for a transfusion. A further specification was made in coronary artery bypass grafting and non-coronary artery bypass grafting-related major and minor bleeding. Thrombocytopenia was defined as a thrombocyte count $<100{,}000/mm^3$, whereas the patient had to have a thrombocyte count within the normal range on admission normal thrombocyte count between 150,000 to $450{,}000/mm^3$.

Angiographic core laboratory. All angiographic parameters were analyzed by an independent core laboratory (Diagram BV, Zwolle, the Netherlands). The infarct-related vessel was identified by the core laboratory technician, based both on electrocardiographic localization of ischemia and angiographic appearance of the lesion. Grading of infarct-related vessel flow was performed according to the Thrombolysis In Myocardial Infarction (TIMI) classification (15). In case of any doubt, a second investigator assessed flow of the infarct-related vessel, and consensus was achieved in all cases. The corrected TIMI frame count and the myocardial blush grade after angioplasty were defined as previously described (16,17).

Statistical analysis. Baseline characteristics were summarized using descriptive statistics. Results are expressed as mean values ± SD. Differences between group means were tested by analysis of variance. A chi-square method or Fisher exact test was used to test differences between proportions. The Fisher exact test was used if there was an expected cell value <5. Statistical significance was defined as a p value <0.05.

In order to assess a possible relationship of platelet aggregation inhibition and PCI success, the post-PCI aggregation measurements from all patients were combined, and the mean extent of platelet aggregation inhibition between patients with successful versus unsuccessful PCI was compared. Successful PCI was defined as TIMI flow grade 3 and myocardial blush grade 3 or as a corrected TIMI frame count <14.

RESULTS

Patient characteristics. Between August 1, 2002, and February 7, 2003, 119 patients were randomized before angiography. Baseline characteristics are shown in Table 1. No significant differences were seen between the four treatment groups. Mean age was 61 years, and 76% was male. Seven patients did not undergo a PCI, four patients underwent coronary artery bypass surgery, and three patients were treated conservatively. Therefore, the final study population consisted of 112 patients.

Platelet aggregation inhibition. Assessment of platelet aggregation inhibition was performed in 89% to 94% of patients at four different time points. At baseline, the mean extent of platelet aggregation inhibition was 21.0% in the clopidogrel only, 16.9% in the abciximab, 15.1% in the tirofiban, and 15.9% in the high-dose tirofiban group. Immediately after PCI, these values were 17.6%, 45.9%, 58.6%, and 84.2%, respectively. One hour after PCI, the mean extent of platelet aggregation inhibition was 42.4%, 53.2%, 57.3%, and 74.5%. Finally, 6 h after PCI, the mean platelet aggregation inhibition was 40.0%, 55.7%, 71.9%, and 64.1% for the four different groups. Results were highly variable for individual patients and suboptimal for all agents,

Table 1. Baseline Characteristics of the Four Treatment Groups

	C (n = 30)	C + A (n = 30)	C + T (n = 30)	C + HT (n = 29)
Age (mean ± SD)	59.8 ± 11.3	62.5 ± 10.8	60.2 ± 15.3	61.8 ± 10.6
Male gender (%)	80	67	83	72
Referral center (%)	47	57	40	45
Hypertension (%)	27	43	37	41
Diabetes (%)	13	20	7	7
Smoking (%)	60	52	39	31
Hypercholesterolemia (%)	22	28	47	15
Family history (%)	41	50	54	43
Previous MI (%)	3	7	13	3
Previous PCI (%)	3	7	7	10
Previous CABG (%)	0	3	7	0
Previous CVA (%)	3	0	3	0
Ischemic time (mean [min] ± SD)	253 ± 171	277 ± 205	242 ± 142	287 ± 252
Time to first sample (mean [min] ± SD)*	46.3 ± 31	17.1 ± 12.9	31.4 ± 16.3	24.8 ± 23.8

*The difference between C and C + A was statistically significant; however, this was largely due to the fact that the oral dose of clopidogrel was given shortly after admission in the emergency room and the glycoprotein IIb/IIIa inhibitors were given not earlier than after angiography.

C = clopidogrel; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; C + A = clopidogrel + abciximab; C + HT = clopidogrel + high-dose tirofiban; C + T = clopidogrel + tirofiban; MI = myocardial infarction; PCI = percutaneous coronary intervention; Referral center = admitted in tertiary hospital via referral center; Time to first sample = time from study drug bolus or clopidogrel loading dose (the latter for group treated with clopidogrel only) to first sample draw (i.e., "after PCI" specimen).

particularly in the periprocedural period. In the periprocedural period, the mean platelet aggregation inhibition was significantly higher in the high-dose tirofiban regimen compared with any of the other regimens, and there was no significant difference between the standard dose tirofiban and abciximab regimen. Only in the high-dose tirofiban regimen, the mean periprocedural platelet aggregation inhibition exceeded 80%. With the standard dose tirofiban and abciximab regimen, the platelet aggregation inhibition increased over the 6 h after PCI, but the difference was not statistically significant (standard dose tirofiban regimen: $p = 0.058$; abciximab regimen: $p = 0.720$). For the high-dose tirofiban regimen, the platelet aggregation inhibition decreased over the 6 h after PCI, but also this difference was not statistically significant ($p = 0.085$). The results of the assessment of the extent of platelet aggregation inhibition for the four different treatment groups are shown in Table 2.

The TIMI flow after the procedure could be assessed in

Table 2. Mean Platelet Aggregation Inhibition (%) ± SD at Four Different Time Points

	C (n = 27)	C + A (n = 28)	C + T (n = 29)	C + HT (n = 28)
Baseline	21.0 ± 23.8	16.9 ± 22.8	15.1 ± 22.1	15.9 ± 20.2
After PCI	17.6 ± 22.3	45.9 ± 29.8	58.6 ± 28.9	84.2 ± 16.1
1 h after PCI	42.4 ± 33.8	53.2 ± 26.4	57.3 ± 26.9	74.5 ± 16.7
6 h after PCI	40.0 ± 31.6	55.7 ± 25.5	71.9 ± 17.3	64.1 ± 22.2

		p Value
Baseline	All comparisons	NS
After PCI	C versus C + A	0.001
	C versus C + T	< 0.001
	C versus C + HT	< 0.001
	C + A versus C + T	NS
	C + A versus C + HT	< 0.001
	C + T versus C + HT	0.002
1 h after PCI	C versus C + A	NS
	C versus C + T	NS
	C versus C + HT	< 0.001
	C + A versus C + T	NS
	C + A versus C + HT	0.025
	C + T versus C + HT	NS
6 h after PCI	C versus C + A	NS
	C versus C + T	< 0.001
	C versus C + HT	0.006
	C + A versus C + T	NS
	C + A versus C + HT	NS
	C + T versus C + HT	NS

Abbreviations as in Table 1.

Table 3. Angiographic Parameters and Relationship With IPA

	C (n = 27)*	C + A (n = 28)*	C + T (n = 29)*	C + HT (n = 28)*
TIMI flow grade 3 (%)	85	92	86	86
CTFC ± SD	22.4 ± 10.1	23.2 ± 8.9	28.2 ± 18.9	24.2 ± 16.0
MBG 3 (%)	54	32	35	52

	CTFC < 14 (n = 18)	CTFC ≥ 14 (n = 63)	p Value
Mean IPA (± SD) after PCI	60.6 ± 34.6	54.9 ± 33.7	0.548
Mean IPA (± SD) 1 h after PCI	61.1 ± 28.4	56.9 ± 27.7	0.581
Mean IPA (± SD) 6 h after PCI	65.4 ± 21.4	63.6 ± 23.9	0.782

	MBG 3 (n = 46)	MBG < 3 (n = 63)	p Value
Mean IPA (± SD) after PCI	52.6 ± 36.7	53.5 ± 32.3	0.888
Mean IPA (± SD) 1 h after PCI	54.7 ± 30.7	59.3 ± 26.5	0.416
Mean IPA (± SD) 6 h after PCI	56.0 ± 30.4	58.7 ± 24.3	0.633

*For all comparisons: p = NS.

CTFC = corrected TIMI frame count; IPA = platelet aggregation inhibition; MBG = myocardial blush grade; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

110 of 112 patients who underwent PCI (98%). Myocardial blush grade after PCI could be assessed in 107 of 112 patients (96%). The results of the angiographic parameters after PCI are shown in Table 3. No significant differences were seen between the four treatment groups for any of the assessed parameters. In the total group of 112 patients, no relationship could be demonstrated between the extent of platelet aggregation inhibition immediately after PCI and angiographic parameters of reperfusion (Table 3).

No patient suffered from reinfarction during hospital stay. Only one patient died during hospitalization (high-dose tirofiban regimen). The total incidence of major and minor bleeding complications during admission was 13%. No patients suffered from intracerebral hemorrhage or died because of bleeding during admission. In the 12 patients (10%) with major bleeding, five cases were related to coronary artery bypass grafting. In the remaining seven patients with major bleeding, three patients (3%) suffered from a serious groin hematoma/bleeding. In three other patients, no bleeding site could be found despite additional diagnostic tests. One patient suffered from major bleeding caused by a perforating gastric ulcer, for which urgent abdominal surgery had to be performed. The total incidence of thrombocytopenia during admission was 5%. A summary of major and minor bleeding complications and the incidence of thrombocytopenia for each treatment group is given in Table 4.

DISCUSSION

This study showed that, in the majority of patients with STEMI undergoing PCI and treated with different antiplatelet agents, platelet aggregation inhibition is suboptimal. Furthermore, the data show that the extent of platelet aggregation inhibition is highly variable in individual patients and varies considerably within each regimen at all time points of assessment. Only with the high-dose tirofiban regimen, the extent of periprocedural inhibition of platelet aggregation reached a mean level >80%.

It, therefore, shows that, in high-risk patients with STEMI undergoing PCI, in the setting of a large thrombogenic and inflammatory stimulus, a higher dose of GP IIb/IIIa inhibitor may be necessary to achieve sufficiently high levels of inhibition. It is known that platelets are activated mostly by agents like thrombin and collagen, which might result in an increase of the amount of activated GP IIb/IIIa receptors by as much as 50% (18). In patients with an acute STEMI, (occlusive) thrombus is present in the vast majority of patients, and, therefore, these patients are expected to have the highest extent of platelet activation, as compared with patients with stable angina or patients with acute coronary syndromes without ST-segment elevation.

Our observations support the findings of previous smaller studies that found substantial interpatient variability in

Table 4. Bleeding Complications and Thrombocytopenia During Admission

	C (n = 30)	C + A (n = 30)	C + T (n = 30)	C + HT (n = 29)
Major	2	0	8	2
CABG-related	1	0	3	1
Minor	1	2	0	1
CABG-related	1	0	0	0
Thrombocytopenia	2	1	2	1
CABG-related	1	0	0	1

Statistical Analysis According to the Incidence of Major Bleeding	
C + A versus C + T	p = 0.002
C + A versus C	p = 0.237
C + A versus C + HT	p = 0.237
C + T versus C	p = 0.037
C + T versus C + HT	p = 0.037
C versus C + HT	p = 1.000

CABG-related = related to coronary artery bypass grafting; other abbreviations as in Table 1.

response to treatment with GP IIb/IIIa inhibitors (1,19–21). Indirect evidence from several placebo-controlled trials of GP IIb/IIIa inhibitors in PCI has suggested the importance of achieving and maintaining a specific level of platelet inhibition to minimize thrombotic complications (22). In our study, only a very small number of patients had levels of inhibition of platelet aggregation >95%, the level that is assumed to be associated with a decrease in the incidence of major cardiac events after PCI (1). The "debate on the dosage" continues, as it is still unknown which "target" level is needed for patients with STEMI undergoing PCI. Although a higher level of periprocedural platelet aggregation inhibition was observed in the high-dose tirofiban regimen, this was not associated with a better angiographic outcome. The other way around, no relationship was found between success of the PCI (TIMI frame count <14 or myocardial blush grade 3) and the extent of platelet aggregation inhibition when the data of all 112 patients were combined. Therefore, it remains to be studied whether platelet aggregation testing is clinically useful and whether further dose-adjustment of antiplatelet agents will further improve angiographic or clinical outcome.

Furthermore, this study showed that platelet aggregation inhibition increases over time after the oral administration of 300 mg of clopidogrel. However, only at 1 h after PCI, a measurable increase in platelet inhibition was found. This implicates that, in patients with acute myocardial infarction in which the PCI should be performed as soon as possible, an oral dose of clopidogrel alone might not give sufficient platelet aggregation inhibition during the PCI procedure. Previous studies showed that clopidogrel at a loading dose of 600 mg results in sufficient platelet aggregation inhibition within 2 h after ingestion; however, whether these results are reproducible in patients with an acute myocardial infarction remains to be evaluated (23).

Only a few patients suffered from a major bleeding complication or a thrombocytopenia during admission, and, although the rate of major complications is higher in the standard dose tirofiban group, these complications were not specifically related to the high-dose tirofiban regimen in particular. Our results are in accordance with earlier observations during treatment with (high-dose bolus) tirofiban (11,12).

Study limitations. Platelet aggregation inhibition was assessed using one evaluation method. Although we validated the blood cell counter, by showing a correlation coefficient of 0.90 with the ICHOR point-of-care platelet analyzer (Helena Laboratories), our results may not be directly comparable with the absolute levels of platelet aggregation inhibition seen in the AU-Assessing Ultegra (GOLD) trial, in which the ultegra rapid platelet function analyser (Accumetrics Inc., San Diego, California) was used for evaluation of platelet aggregation inhibition (1,13,14,24). However, this does not affect differences in measurements of platelet aggregation inhibition between the four treatment groups. Secondly, the sample size in our study was too small to demonstrate differences in outcome. Finally, we evaluated two different tirofiban dose regimens and no other abciximab dose regimen than the currently used dosage scheme.

This study assessed periprocedural platelet aggregation inhibition only at one time point (immediately after PCI). No information is available on platelet inhibition just before PCI, or between 25 and 85 min after the administration of study drug, which is a shortcoming of the study.

Conclusions. The extent of platelet aggregation inhibition in patients with STEMI undergoing PCI and treated with different antiplatelet agents is highly variable and suboptimal for all agents and dosages studied. Only with the high-dose tirofiban regimen, the mean periprocedural level of platelet aggregation inhibition exceeded 80%. However, no difference in angiographic outcome between the groups was found, and no relationship was found between the level of platelet aggregation inhibition and angiographic outcome when the data of all groups were combined. Therefore, further studies should be performed to assess whether dose adjustment or combination therapy of different antiplatelet agents will further improve clinical outcome.

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