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Value of Platelet Reactivity in Predicting Response to Treatment and Clinical Outcome in Patients Undergoing Primary Coronary Intervention

Insights Into the STRATEGY Study

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OBJECTIVES The purpose of this study was to evaluate the value of platelet reactivity (PR) in predicting the response to treatment and outcome in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention assisted by glycoprotein (GP) IIb/IIIa inhibition.

BACKGROUND There is limited prognostic information on the role of spontaneous or drug-modulated PR in STEMI patients.

METHODS The PR was measured with Platelet Function Analyzer (PFA)-100 and light transmission aggregometry (LTA) using adenosine diphosphate as agonist in 70 consecutive STEMI patients at entry (PR-T0), 10 min after GP IIb/IIIa bolus (PR-T1), and discharge (PR-T2) and in 30 stable angina (SA) patients (PR-SA). Complete platelet inhibition (CPI) was based on closure time >300 s by PFA-100 and percentage inhibition of platelet aggregation >95% by LTA. Clinical, electrocardiographic, and angiographic responses to treatment during 1-year follow-up were collected.

RESULTS According to both techniques, PR-T0 was higher than: 1) PR-T2 and PR-SA; 2) in those without CPI at T1; and 3) in patients with final Thrombolysis In Myocardial Infarction (TIMI) flow grade <3. The PR-T0 assessed with PFA-100 correlated with: 1) corrected TIMI frame count ($r = -0.6$, $p < 0.001$); 2) ST-segment resolution ($r = 45$, $p < 0.001$); and 3) creatine kinase-MB ($r = -0.47$, $p < 0.001$). At 1 year, patients with high PR-T0 showed an adjusted 5- to 11-fold increase in the risk of death, reinfarction, and target vessel revascularization (hazard ratio [HR] 11, 95% confidence interval [CI] 1.5 to 78 [$p = 0.02$] in PFA-100; HR 5.2, 95% CI 1.1 to 23 [$p = 0.03$] in LTA).

CONCLUSIONS The PR at entry affects response to GP IIb/IIIa inhibition, mechanical treatment, and long-term outcome in STEMI patients undergoing primary intervention. (J Am Coll Cardiol 2006;48:2178–85) © 2006 by the American College of Cardiology Foundation

Platelet activation, by favoring thrombus formation and coronary artery occlusion, is thought to play a key pathogenetic role in acute myocardial infarction. Percutaneous coronary intervention (PCI) is currently considered the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI) (1). Recent evidence strongly argues in favor of glycoprotein (GP) IIb/IIIa inhibition in this setting (2) and reinforces the concept that platelet reactivity (PR) is a potential target of treatment beyond pure mechanical intervention.

In previous studies, PR has been used to evaluate the risk of adverse events (3) and the extent of myocardial necrosis (4). Moreover, the importance of achieving a high level of platelet inhibition early after GP IIb/IIIa bolus in non-STEMI patients has been reported (5).

Whether baseline and/or drug-modulated PR influences response to treatment and myocardial injury in STEMI patients undergoing primary PCI with GP IIb/IIIa inhibition is unknown. This might further extend the current paradigm linking platelet activation to outcome in the STEMI population.

To explore this hypothesis, PR was measured before, during, and after treatment as part of a pre-specified substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) trial (6–7). To address the issue whether high baseline PR is a hallmark of clinical acuity, a matched population affected by stable angina (SA) was also investigated.

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Abbreviations and Acronyms

CADP-CT = cartridge ADP closure time
CPI = complete platelet inhibition
LTA = light transmission aggregometry
PA = platelet aggregation
PCI = percutaneous coronary intervention
PR = platelet reactivity
SA = stable angina
STEMI = ST-segment elevation myocardial infarction

METHODS

Study population. One hundred patients treated with PCI in the catheterization laboraty of the University Hospital of Ferrara were enrolled. The study population comprised 70 consecutive patients (68% male, mean age 63 ± 12 years) with STEMI (STEMI group) enrolled in a previously reported trial (6) and 30 age- and gender-matched patients with SA (SA group) treated with PCI (67% male, mean age 64 ± 6 years) (Table 1). The study was approved by the local ethics committee, and all patients gave written informed consent.

Medications, procedures, and assays. The design of the STRATEGY trial has been previously reported (6–7). Briefly, patients with STEMI were randomly assigned to single high-dose bolus (SHDB) tirofiban (25 μg/kg/3 min, followed by an infusion of 0.15 μg/kg/min for 18 to 24 h) or abciximab (bolus of 0.25 μg/kg/3 min, followed by a 12-h infusion 0.125 μg/kg/min). The study drug was started in the intensive cardiac care unit. Per protocol, patients randomized to tirofiban received sirolimus-eluting stents (SES), whereas those allocated to abciximab received bare-metal stents (BMS). All patients received aspirin (250 mg intravenously followed by 100 mg/day), clopidogrel (300 mg followed by 75 mg/day), heparin (50 to 70 U/kg with additional bolus if necessary), and other treatments as suggested by current guidelines. Patients with SA were treated with aspirin and received, at least 6 h before procedure, 300 mg of clopidogrel.

Angiographic analysis. The angiographic images were acquired with a General Electric Advantage CRS V 5.6.5 (Fairfield, Connecticut) single-plane system at a cine rate of 25 frames/s before and immediately after the procedure. Angiograms were analyzed by 1 experienced interventional cardiologist blinded to the platelet assay results. All angiograms were assessed with a respect to Thrombolysis In Myocardial Infarction (TIMI) flow scale in the infarct-related artery (IRA) at baseline and after PCI (8). The corrected TIMI frame counts (CTFC) and the myocardial blush grade (MBG) were determined on a final angiogram as described previously (9–10). No reflow was defined as TIMI flow grade 0 or I despite successful ballon angioplasty or stent insertion, in spite of residual stenosis <50%, absence of significant dissection, or visible thrombus or spasm in the IRA. Procedural success was defined as the achievement of a final <30% residual stenosis and TIMI flow grade 3.

Blood sample collection. In the STEMI group, 3 blood samples were performed: at entry (T0) before treatment, 10 (±1) min after the GP IIb/IIIa inhibitors bolus (T1), and at discharge (T2) (7 ± 3 days). In the SA group, blood was drawn before PCI procedure and clopidogrel intake (T0).

Platelet function testing. Platelet function was measured with Platelet Function Analyzer-100 (PFA-100) (Dade Behring, Miami, Florida), a U.S. Food and Drug Administration-approved device, and with light transmission aggregometry (LTA).

PFA-100. In the PFA system (11) blood is forced to flow throughout a synthetic capillary (147 μm diameter), with a collagen and adenosine 5′-diphosphate (ADP)–coated membrane with a central hole at its end (CADP cartridge, 50 μg ADP and 2 μg type 1 equine collagen). When a

Table 1. Baseline Characteristics of the Patients

Characteristic	SHDB Tirofiban Group (n = 35)	Abciximab Group (n = 35)	p Value	STEMI Group (n = 70)	SA Group (n = 30)	p Value
Age (yrs)	64 ± 13	63 ± 12	0.6	63 ± 12	64 ± 6	0.3
Men, n (%)	22 (63)	26 (74)	0.2	48 (68)	20 (67)	0.5
Diabetes, n (%)	7 (20)	6 (17)	0.5	13 (18)	6 (20)	0.5
Hypertension, n (%)	23 (66)	21 (60)	0.4	44 (63)	20 (66)	0.4
Smoker, n (%)	10 (28)	16 (46)	0.1	26 (37)	11 (36)	0.6
Medical history						
CABG, n (%)	0 (0)	0 (0)	>0.9	0 (0)	2 (6)	0.09
PCI, n (%)	0 (0)	1 (3)	0.5	1 (1.5)	0 (0)	0.7
Acute myocardial infarction, n (%)	2 (6)	2 (6)	0.7	4 (6)	4 (13)	0.2
Laboratory values at entry						
Platelet count (U/ml)	241 ± 45	254 ± 100	0.5	247 ± 97	251 ± 91	0.8
Hematocrit (%)	40 ± 5	41 ± 4	0.2	41 ± 5	42 ± 6	0.6
White blood count (U/ml)	11.9 ± 4	12.1 ± 3	0.8	12 ± 4	8 ± 3	<0.01
Fibrinogen (mg/dl)	420 ± 162	395 ± 116	0.4	407 ± 139	400 ± 129	0.7
Creatinine clearance (ml/min)	85 ± 38	84 ± 28	0.9	85 ± 33	82 ± 28	0.8

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SA = stable angina; SHDB = single high-dose bolus; STEMI = ST-segment elevation myocardial infarction.

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hemostatic platelet plug completely obliterates the central hole, the blood flow stops. The time necessary to stop the flow is called "closure time" (CADP-CT) and inversely reflects platelet reactivity. Its reference range in the absence of antiplatelet therapy is 69 to 130 s (11–12). This instrument confines detection of closure to a 300-s window and, as a result, "nonclosure" is obtained. This degree of platelet inhibition corresponds to >90% inhibition of platelet aggregation by means of light transmission aggregometry (20 μmol/l ADP) (12–13). The CADP cartridge was selected in the present study to monitor the effect of GP IIb/IIIa inhibitors on platelet function based on available evidence (12,13).

LIGHT TRANSMISSION AGGREGOMETRY. Blood was centrifuged (200 *g* × 10 min) to obtain platelet-rich plasma (PRP). The platelet count in PRP was adjusted to the range of 150,000 to 300,000/l by dilution with autologous plasma when out of range. The remaining specimen was recentrifuged (1,500 *g* × 15 min) to obtain platelet-poor plasma (PPP). Platelets were stimulated with 20 μmol/l ADP. Aggregation was measured at 37°C with a PACKS-4 Aggregometer (Helena Laboratories, Beaumont, Texas) and expressed as the maximal percentage change in light transmittance from baseline at 5 min after the addition of the agonist, with PPP as a reference. Percentage inhibition of platelet aggregation (%IPA) was determined by the following formula: (%PA at baseline − %PA 10 min after GP IIb/IIIa)/%PA at baseline.

All samples for analysis were collected into evacuated tubes containing 3.8% trisodium citrate and in evacuated tubes containing D-Phe-Pro-Arg-chloromethylketone (PPACK). All measurements were done 0.5 to 1 h after blood sampling. The CADP-CT measurements with citrate and PPACK were highly correlated ($r = 0.96$, $p < 0.001$). Coefficients of variation for duplicate analysis averaged 4%. At baseline, CADP-CT correlated with aggregability measured with LTA ($r = -0.95$, $p < 0.001$). All patients who failed to achieve nonclosure at T1 showed %IPA <95%. Complete platelet inhibition (CPI) was defined as CADP-CT >300 s (nonclosure) and %IPA >95%.

Study end points. To test the role of spontaneous and drug-modulated PR, platelet function was related to: 1) angiographic evaluation (TIMI flow grade, incidence of no reflow, CTFC, MBG, and procedural success rate); 2) extent of myocardial necrosis; 3) ST-segment resolution; and 4) clinical outcome. Extent of myocardial necrosis was assessed by creatine kinase-MB (CK-MB) (ng/dl) and troponin I (TnI) (ng/dl) at peak. Cumulative ST-segment elevation, evaluated in all leads with any ST-segment elevation ≥1 mm, was measured to the nearest 0.5 mm at 60 min after the J point with the aid of hand-held calipers. The clinical end points were death, reinfarction, target vessel revascularization (TVR) (major adverse cardiac events [MACE]), and angiographically confirmed stent thrombosis (ST).

Statistical analysis. Continuous data are presented as mean values ± SD, with the significance of differences judged by *t* test. Because results of PFA-100 and LTA were both not normally distributed by Kolmogorov-Smirnov goodness-of-fit test, the Mann-Whitney test was used to compare PR values between groups. Kruskal-Wallis analysis of variance was used to compare more than 2 groups of patients and to generate p values for trend tests for the distribution of CK-MB and troponin levels according to platelet reactivity quartiles. Categoric variables were summarized in terms of number and percentages and were compared using 2-sided Fisher exact test. Spearman's correlation coefficients were used to detect any association between variables. Linear regression analysis was used to test association between PR and variables reported in Table 1. Survival curves were constructed by the Kaplan-Meier method, and survival among groups was compared using the log rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariate analysis, considering all clinical or angiographic variables differently distributed (using $p < 0.10$ as a threshold) according to median value of CADP-CT at entry, was performed to identify whether PR is an independent predictor for adverse events at 1 year. Probability was considered to be significant at a level of <0.05. Analysis was performed using Statistica 6.1 (Statsoft, Tulsa, Oklahoma).

RESULTS

Baseline and procedural data of the study population are shown in Tables 1 and 2. Patients with SA, recruited in February to March 2004, were well matched for age, gender, and all risk factors with respect to STEMI patients. Between January and April 2004, 70 STEMI patients, randomly allocated to receive tirofiban or abciximab, were prospectively enrolled in the present analysis. Their baseline and procedural characteristics did not differ from those enrolled in the cohort of the STRATEGY trial (6). Sixty-six patients (94%) were treated with stent implantation, and 1 patient per group received only balloon angioplasty. In 1 patient in the SHDB tirofiban group, coronariography was not followed by treatment owing to both prompt restoration of TIMI flow grade 3 after intracoronary nitrates injection and absence of coronary obstruction, whereas in 1 patient in the abciximab group, type I aortic dissection determining occlusion of the right coronary artery was followed by emergent surgery.

Platelet reactivity assays. The PR before any treatment, evaluated in terms of both CADP-CT (76 ± 11) and %PA (90 ± 5) was higher in STEMI than in SA patients (96 ± 6 and 50 ± 6; $p < 0.01$ for both) (Fig. 1). The CADP-CT or %PA at entry was not related to any of the variables in Table 1. At entry, there were no differences between tirofiban and abciximab in terms of CADP-CT (77 ± 11 vs. 74 ± 12; $p = 0.3$) or %PA (89 ± 4 vs. 90 ± 4; $p = 0.5$) (Fig. 1). Overall, 4 patients were assuming aspirin as chronic

Table 2. Procedural Data

Characteristic	SHDB Tirofiban Group (n = 35)	Abciximab Group (n = 35)	p Value	STEMI Group (n = 70)	SA Group (n = 30)	p Value
Treated artery, n (%)						
Left anterior descending	10 (29)	17 (49)	0.07	27 (40)	14 (47)	0.3
Right coronary	15 (44)	13 (38)	0.4	28 (41)	6 (20)	0.04
Circumflex	9 (27)	4 (13)	0.1	13 (19)	10 (33)	0.4
GP IIb/IIIa-to-balloon (min)	35 ± 7	37 ± 10	0.7	36 ± 10	—	—
PCI successful, n (%)	30 (88)	31 (92)	0.5	61 (88)	30 (100)	0.07
Reference diameter, pre (mm)	2.7 ± 0.6	2.8 ± 0.5	0.7	2.7 ± 0.5	2.8 ± 0.6	0.6
Total stent length (mm)	27 ± 17	29 ± 15	0.6	28 ± 16	30 ± 15	0.2
Nominal stent diameter (mm)	3 ± 0.5	3 ± 0.4	0.6	3 ± 0.4	3 ± 0.7	0.8
Stent implantation, n (%)	33 (94)	33 (94)	0.7	66 (94)	30 (100)	0.2
TIMI flow, n (%)						
Preprocedure						
Grade 0 or 1	28 (80)	30 (86)	0.4	58 (83)	0 (0)	<0.01
Grade 2	5 (14)	4 (11)	0.5	9 (13)	8 (27)	0.08
Grade 3	2 (6)	1 (3)	0.5	3 (4)	22 (73)	<0.01
Postprocedure						
Grade 0 or 1	2 (6)	1 (3)	0.5	3 (4)	0 (0)	0.3
Grade 2	1 (3)	2 (6)	0.7	3 (4)	0 (0)	0.2
Grade 3	31 (91)	31 (91)	0.5	62 (91)	30 (100)	0.07
No reflow, n (%)	2 (6)	1 (3)	0.5	3 (4)	0 (0)	0.3
Σ ST-segment resolution >50%, n (%)	31 (88)	29 (83)	0.3	60 (86)	—	—
Σ ST-segment resolution >70%, n (%)	20 (57)	17 (48)	0.3	37 (53)	—	—
CK-MB at peak (ng/ml)	210 ± 187	227 ± 154	0.7	218 ± 170	—	—
Troponin I at peak (ng/ml)	85 ± 77	108 ± 95	0.3	97 ± 87	—	—

GP IIb/IIIa = start of GP IIb/IIIa inhibitors; Σ = cumulative; other abbreviations as in Table 1.

treatment before entry. Their PR did not differ in terms of PFA-100 or LTA at T0 or T1 compared with aspirin-naive patients.

At T1, 31 of 35 patients (89%) treated with tirofiban versus 30 of 35 (86%) receiving abciximab reached the CPI (p = 0.5). In the remaining 9 patients, CADP-CT was 298 s (297 to 299 s) in the 4 who received tirofiban and 294 s (292 to 296 s) in the 5 who received abciximab (p = 0.06), whereas %PA was 11 ± 2 vs. 14 ± 4 (p = 0.3), respectively. In these 9 patients, baseline PR was significantly higher than in those reaching CPI at T1 (CADP-CT: 65 ± 12 vs. 77 ± 10, p = 0.002; %PA: 93 ± 4 vs. 89 ± 4, p = 0.003). Out of all variables included in Table 1, only PR at T0 was related to PR at T1. At discharge (7 ± 3 days), PR was lower than at entry in the STEMI group (CADP-CT: 76 ± 11 vs. 98 ± 8; p < 0.001), which was confirmed by LTA findings (Fig. 1).

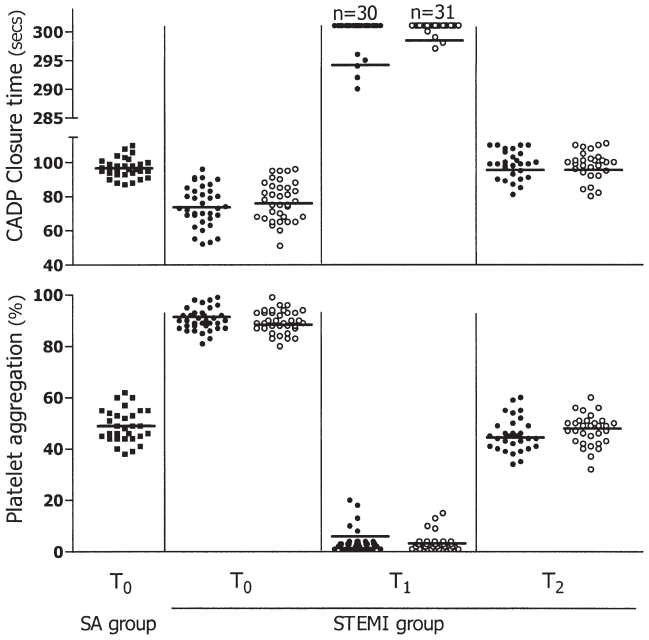

Figure 1. Platelet reactivity assays. **Solid squares** = patients with stable angina (SA); **open squares** = patients with ST-segment elevation myocardial infarction (STEMI); **solid circles** = abciximab subgroup; **open circles** = single high-dose bolus (SHDB) tirofiban subgroup. CADP = cartridge adenosine diphosphate closure time; T_0 = baseline; T_1 = 10 min after glycoprotein IIb/IIIa bolus; T_2 = discharge.

Platelet reactivity and angiographic data. Baseline PR, measured as CADP-CT and %PA (Fig. 2), was higher in patients with TIMI flow grade 0/1 compared with those with TIMI flow grade 2/3 at first angiogram (p < 0.001 for both). Among patients in whom angioplasty was attempted (68 patients), procedural success was reached in 61 (90%): In 3 patients, a final TIMI flow grade 2 was obtained despite repeated administration of intracoronary vasodilatators; in another 3, an irreversible no-reflow phenomenon after stent implantation was observed; and in the remaining patient, a distal macroembolization in a posterolateral branch occurred after vessel wiring. In these 7 patients, baseline CADP-CT was lower (66 ± 7 vs. 77 ± 11; p = 0.01) and %PA higher (93 ± 4 vs. 89 ± 4; p = 0.02) than in those with procedural success. Four (44%) of the 9 patients who failed to achieve the CPI at T1 had an unsuccessful intervention compared with 3 (5%) in whom maximum platelet inhibition was obtained (p = 0.004).

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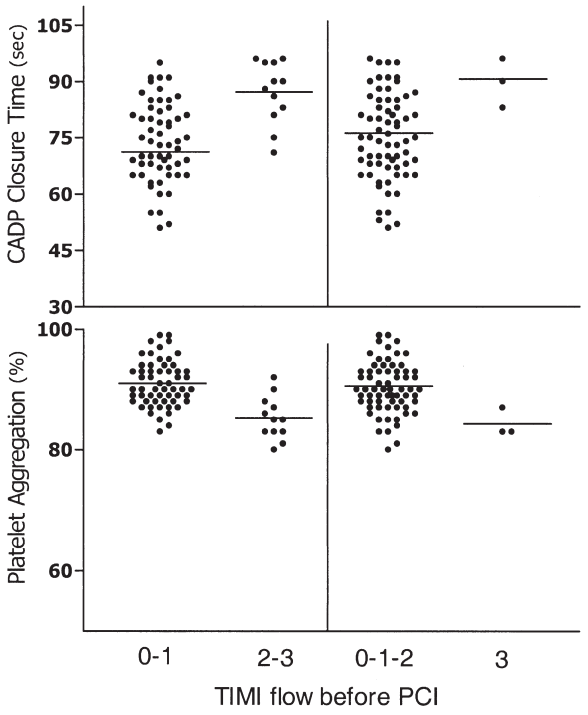

Figure 2. Relationship between Thrombolysis In Myocardial Infarction (TIMI) flow grade before percutaneous coronary intervention (PCI) and baseline cartridge adenosine diphosphate (CADP) closure time (CADP-CT). Lower TIMI flow at first angiogram was associated with higher platelet reactivity (PR). CADP-CT was 73 ± 11 in the TIMI flow grade 0/1 group versus 87 ± 8 in the TIMI flow grade 2/3 group ($p < 0.001$), and % platelet aggregation was, respectively, 91 ± 4 versus 85 ± 3 ($p < 0.001$). CADP-CT was 75 ± 11 in the TIMI flow grade 0/1/2 group versus 89 ± 6 in the TIMI flow grade 3 group ($p = 0.03$), and %PA was, respectively, 90 ± 4 versus 84 ± 2 ($p = 0.01$).

Patients showing no reflow had enhanced PR (CADP-CT: 62 ± 7 vs. 77 ± 11, $p = 0.03$; %PA: 95 ± 3 vs. 89 ± 4, $p = 0.02$). None of them reached the CPI at T1. The CADP-CT and %PA at entry was related to CTFC both in all patients receiving intervention ($r = -0.6$, $p < 0.001$) and in those with final TIMI flow grade 3 ($r = -0.53$, $p < 0.001$). Patients with MBG 2/3 tended to have lower PR compared with those with MBG 0/1 (CADP-CT: 77 ± 11 vs. 71 ± 11, $p = 0.06$; %PA: 89 ± 5 vs. 91 ± 4, $p = 0.05$).

Platelet reactivity and ST-segment resolution. The CADP-CT and %PA at baseline was directly correlated to the degree of ST-segment resolution immediately after the procedure ($r = 0.45$ and $r = -0.42$, respectively; $p < 0.001$ for both). The PR at entry was higher in patients without cumulative ST-segment resolution >50% (CADP-CT: 67 ± 10 vs. 78 ± 11, $p = 0.001$; %PA: 93 ± 4 vs. 89 ± 4, $p = 0.003$) or >70% (CADP-CT: 72 ± 11 vs. 80 ± 11, $p = 0.007$; %PA: 91 ± 4 vs. 88 ± 3, $p = 0.006$). Four (44%) and seven (78%) among the 9 patients who failed to achieve CPI did not reach ST-segment resolution >50% or >70% compared with 7 (12%) and 24 (41%) of the 59 with CPI ($p = 0.03$ and $p = 0.04$, respectively).

Platelet reactivity and infarct size. The CADP-CT at T0 was inversely correlated with CK-MB and TnI at peak in patients with STEMI ($r = -0.47$, $p < 0.001$ and $r = -0.48$, $p < 0.001$, respectively). CK-MB and Tn I at peak according to CADP-CT quartiles are shown in Figure 3. All data were confirmed by LTA (data not shown).

Platelet reactivity and clinical outcome. Complete follow-up information up to 365 days was available for all patients. In the SA group, no adverse event was observed. In the STEMI group at 30 days, 3 deaths and 2 reinfarctions occurred owing to subacute ST, which required urgent TVR. At 1 year, 13 patients (18%) experienced adverse events, including 4 deaths, 4 reinfarctions (2 due to ST), and 7 TVR (2 urgent).

At entry, patients with MACE at 30 days, compared with those without, had higher PR at T0 (CADP-CT: 57 ± 8 vs. 77 ± 10, $p < 0.001$; %PA: 97 ± 4 vs. 89 ± 4, $p < 0.001$) (Fig. 4). Of note, the 2 patients who had ST failed to achieve CPI at T1.

Patients with MACE within 1 year had lower CADP-CT at entry (65 ± 9 vs. 78 ± 11; $p < 0.001$) and higher %PA (94 ± 3 vs. 89 ± 4; $p < 0.001$) than those with uneventful follow-up (Fig. 4). The cumulative incidence of MACE was significantly lower in patients with high (above median value, low PR) compared with those with low (below median value, high PR) CADP-CT at T0 (3% vs. 34%; $p = 0.0006$). The patients in the high-reactivity group showed a 12-fold increase in the risk of composite end point (hazard ratio [HR] 12, 95% confidence interval [CI] 2.7 to 125; $p = 0.0009$) (Fig. 5). As shown in Table 3, there were no statistically significant differences between groups with the exception

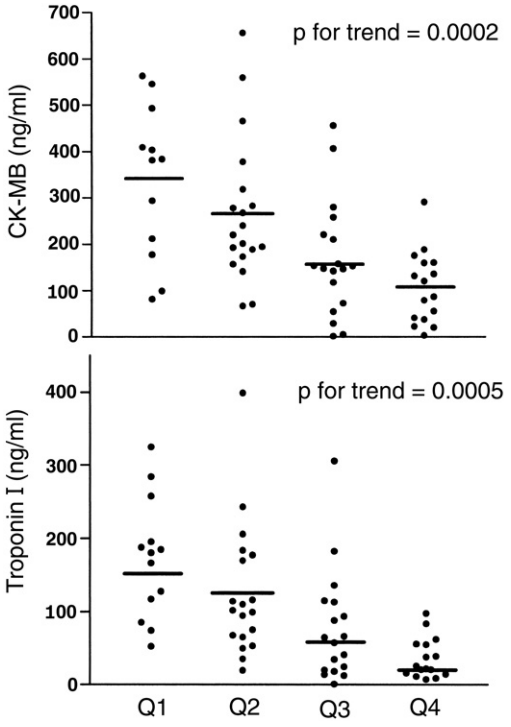

Figure 3. Peak plasma levels of creatine kinase-MB (CK-MB) **(top)** and troponin I **(bottom)** are shown according to quartiles (Q) of CADP closure at admission. CADP-CT = cartridge adenosine diphosphate closure time.

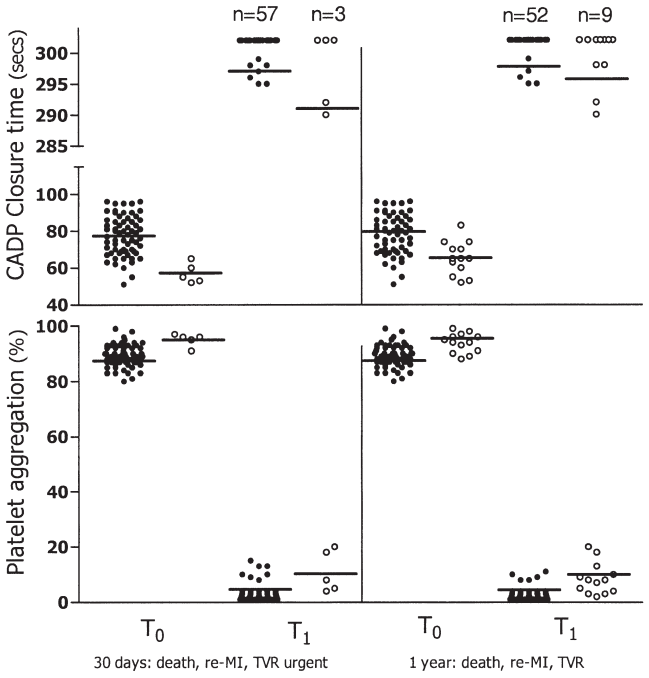

Figure 4. Cartridge adenosine diphosphate (CADP) closure time stratified in relation with the clinical outcome at 30 days and at 1 year. **Solid circles** = patients that not reached the composite end point; **open circles** = patients that reached the composite end point. MI = myocardial infarction; TVR = target vessel revascularization.

of percentage of diabetes mellitus, which was higher in the high-PR subgroup (10% vs. 3%; p = 0.03). Including diabetes, at multivariate analysis PR remained an independent predictor for MACE (HR 11, 95% CI 1.5 to 78; p = 0.02). Based on LTA, there was an adjusted 5-fold increase in the risk of MACE (HR 5.2, 95% CI 1.1 to 23; p = 0.03) in the high-reactivity group.

At discharge, PR tended to be higher in patients with compared with those without adverse events at follow-up (CADP-CT: 94 ± 8 vs. 98 ± 8, p = 0.2; %PA: 18 ± 6 vs. 15 ± 5, p = 0.1).

DISCUSSION

Platelet reactivity is pivotal in the pathogenesis of acute coronary syndromes (ACS) and it is a well known predictor for adverse outcome after PCI (3). Accordingly, inhibitors of GP IIb/IIIa decrease incidence of adverse events both in the PCI setting (14) and in patients with ACS (15).

The three major findings of the present study are:

1. Patients with STEMI have higher PR than patients with SA.
2. Baseline PR affects the response to GP IIb/IIIa inhibitors soon after bolus.
3. The PR at baseline and, consecutively, after GP IIb/IIIa inhibitor bolus influences the angiographic success of the procedure as well as the degree of ST-segment resolution, the extent of myocardial necrosis, and the short- and mid-term clinical outcome in patients undergoing primary intervention.

Our data demonstrated that baseline PR is a hallmark of clinical acuity. This statement is mainly based on the finding that PR was higher in the STEMI than in the control group (patients with SA).

It has been demonstrated that the response to clopidogrel is patient specific, with an important interindividual variability (16–17), and that the pre-treatment platelet activity could influence final response to clopidogrel (17). Recently, 2 case-control studies associated the enhanced platelet

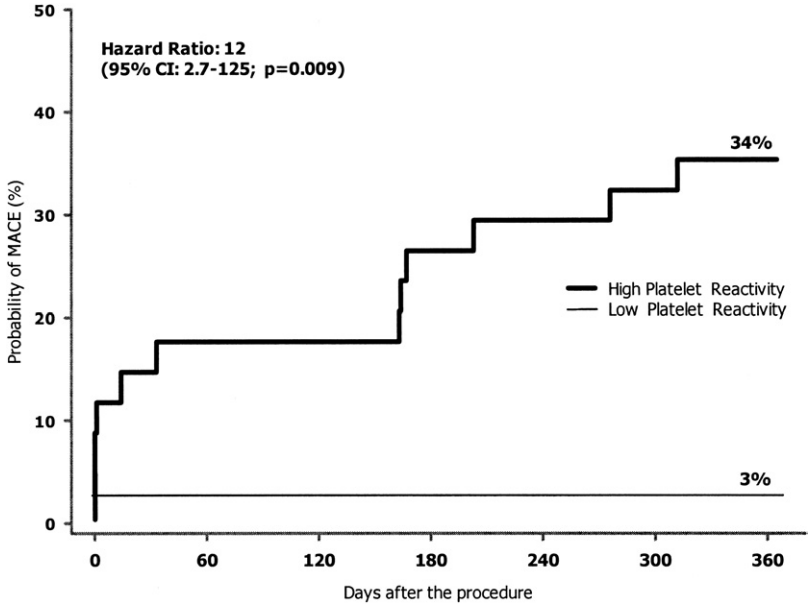

Figure 5. Probability of major adverse cardiac events (MACE) in patients stratified according to PR measured with Platelet Function Analyzer-100. High platelet reactivity = CADP-CT at entry below the median value. Low platelet reactivity = CADP-CT at entry above the median value. Median value of CADP-CT is 75 s. Abbreviations as in Figures 1 and 2.

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Table 3. Clinical, Biochemical, and Procedural Data of STEMI Patients Stratified by Platelet Reactivity at Entry*

Characteristic	High Platelet Reactivity (n = 35)	Low Platelet Reactivity (n = 35)	p Value
Age (yrs)	65 ± 12	62 ± 12	0.4
Men, n (%)	13 (37)	9 (26)	0.2
Diabetes, n (%)	10 (28)	3 (9)	0.03
Hypertension, n (%)	23 (66)	21 (60)	0.4
Smoker, n (%)	12 (35)	14 (39)	0.4
Medical history			
CABG, n (%)	0 (0)	0 (0)	>0.9
PCI, n (%)	0 (0)	1 (3)	0.5
Acute myocardial infarction, n (%)	1 (3)	3 (8)	0.3
Laboratory values at entry			
Platelet count (U/ml)	264 ± 115	232 ± 76	0.2
Hematocrit (%)	40 ± 5	41 ± 4	0.2
White blood count (U/ml)	12.4 ± 4	11.6 ± 3	0.4
Fibrinogen (mg/dl)	392 ± 122	422 ± 155	0.4
Creatinine clearance (ml/min)	82 ± 29	85 ± 35	0.3
Procedural data			
Left anterior descending, n (%)	11 (32)	16 (47)	0.2
Right coronary, n (%)	16 (47)	12 (35)	0.3
Circumflex, n (%)	7 (21)	6 (18)	0.5
Reference diameter, pre (mm)	2.7 ± 0.6	2.8 ± 0.5	0.7
Total stent length (mm)	28 ± 15	28 ± 17	0.9
Nominal stent diameter (mm)	3 ± 0.5	3 ± 0.4	0.6

*High platelet reactivity = closure time (CT) below the median value; low platelet reactivity = CT above the median value; median value of CT at entry is 75 s. Abbreviations as in Table 1.

aggregation and the impaired responsiveness to antiplatelet drugs with the stent thrombosis incidence (18,19). In our prospective study, with a homogeneous patient population in terms of ethnicity (all patients were Caucasian), clinical presentation (STEMI), and treatment (primary PCI), we confirmed that there is an interindividual variability in PR. This influences the response to antiplatelet therapy, also if GP IIb/IIIa inhibitors, the strongest currently available antiplatelet treatment, are used.

Our study population comprised 13 diabetics. In keeping with previous evidence (20), they showed increased PR: At T0, 10 out of 13 (77%) were in the high-PR subgroup ($p = 0.03$ vs. nondiabetics); at T1, using both PFA-100 and LTA, 3 of 13 (23%) achieved incomplete platelet inhibition versus 6 of 57 (11%) in the nondiabetic group ($p = 0.26$); whereas at T_2, CADP-CT in diabetics was lower (91 ± 7 vs. 99 ± 8 in nondiabetics; $p = 0.01$) and %PA higher (19 ± 5 vs. 14 ± 4 in nondiabetics; $p = 0.001$). One of these patients experienced ST at follow-up. Cumulatively, 5 diabetic patients out of 13 (38%) satisfied the composite end point (vs. 14% in nondiabetics; $p = 0.05$). Thus, when taken together with available evidence, the present data suggest that diabetes greatly contributes to overall interindividual variability in PR, and as such diabetics may be an ideal target population for tailored antiplatelet therapy in both acute and chronic settings.

Failure to achieve TIMI flow grade 3, the no-reflow phenomenon, and higher CTFC values after reperfusion therapy have been found to be associated with more extensive myocardial necrosis and poor clinical outcome (21). In the current study, we demonstrated that TIMI flow grade <3, no reflow, and high CTFC occur significantly more frequently in patients with enhanced baseline PR.

As previously reported, the enhanced platelet function correlated with the degree of myocardial damage in the present study (4). Moreover, a clear association between PR and the degree of ST-segment resolution was found. This finding may be critically relevant, because, in STEMI patients treated with primary PCI, ST-segment reduction was independently related to 6-month mortality (2).

In the present study, we studied PR using 2 methodologies. Light transmission aggregometry is still considered to be the gold standard, but it has some disadvantages, such as limited reproducibility and complex sample preparation. Conversely, PFA-100 is a rapid tool that can be used in the clinical practice to identify patients with higher PR, which could potentially be exploited as a means of tailoring the antiplatelet treatment to individual need. This may be particularly relevant in the setting of primary intervention for STEMI, when a short door-to-balloon time is needed and other biomarkers of PR may not available. Further studies are needed to establish the optimal bedside assay to evaluate the PR in this setting.

Study limitations. Owing to limited sample size, our prospective investigation should be regarded as exploratory. In particular, to obtain a reliable estimate of the prognostic capability of PR at entry and to evaluate whether the response to GP IIb/IIIa inhibitors is an independent outcome predictor beyond PR at entry, a larger prospectively collected study population is clearly required. Recently, it has been shown in elective patients that PR measured at least 24 h after stenting independently predicts outcome

(22). In the present study, PR at discharge failed to be significantly associated with outcome; differences in patient selections, timing of platelet assays, and limited statistical power may help explaining these different findings. The PFA-100 confines detection of closure to a 300-s window, and, because in most patients nonclosure is exhibited shortly after GP IIb/IIIa inhibitor administration, this device may be suboptimal for properly identifying those individuals at a higher risk for subsequent thrombotic events. Because this was an issue in the present investigation, future studies with bigger sample size are clearly needed.

Conclusions. In patients undergoing primary PCI for STEMI, PR at entry was related to both angiographic and electrocardiographic response to treatment as well as to the severity of cardiac injury as measured by the release of markers of cardiac necrosis. After 1 year, PR at presentation independently predicted major cardiac adverse events. Whether modulating PR through tailored or systematic antiplatelet treatment overcomes the prognostic implications of spontaneous platelet function remains elusive and may warrant further investigations.

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