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Glycoprotein IIb/IIIa Inhibitors Improve Outcome After Coronary Stenting in Clopidogrel Nonresponders

A Prospective, Randomized Study

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Objectives The aim of this study was to assess, in clopidogrel nonresponders undergoing elective percutaneous coronary intervention (PCI), the benefit of adjusted antiplatelet therapy with glycoprotein (GP) IIb/IIIa antagonist administration during PCI for 1-month clinical outcome.

Background Numerous biological studies have reported interindividual variability in platelet response to clopidogrel with clinical relevance, and high post-treatment platelet reactivity (adenosine diphosphate-induced aggregation >70%) has been proposed to define nonresponse to clopidogrel. These nonresponders might benefit from tailored antiplatelet therapy.

Methods One hundred forty-nine clopidogrel nonresponders referred for elective PCI were prospectively included and randomized to "conventional group" (n = 75) or "active group" with GP IIb/IIIa antagonist (n = 74). All patients received 250-mg aspirin and 600-mg clopidogrel before PCI and platelet testing.

Results The rate of cardiovascular events at 1 month was significantly lower in the "active group" than in the "conventional group": 19% (n = 14) versus 40% (n = 30), p = 0.006, odds ratio: 2.8; 95% confidence interval: 1.4 to 6.0. No patient in either group had post-procedural Thrombolysis In Myocardial Infarction major bleeding or required transfusions.

Conclusions The present study suggested benefit of tailored antiplatelet therapy during elective PCI with GP IIb/IIIa antagonist for clopidogrel nonresponders without increased bleeding risk. (J Am Coll Cardiol Intv 2008;1:649–53) © 2008 by the American College of Cardiology Foundation

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Platelet inhibition with aspirin and clopidogrel has significantly reduced recurrent ischemic events after percutaneous coronary intervention (PCI) and/or non–ST-segment elevation acute coronary syndrome (ACS) (1–3). Nevertheless, ischemic events still occur, and low response to clopidogrel therapy could be a major factor. Numerous biological studies have reported interindividual variability in platelet response to clopidogrel

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with clinical relevance (4–10). Several strategies have been proposed to overcome this variability of response, including higher dose (11), additional loading doses (12), or alternative therapies such as new P2Y12 receptor inhibitors (13). However, no study has ever tested the benefit of glycoprotein (GP) IIb/IIIa antagonist during PCI for clopidogrel nonresponders. Several platelet tests have been proposed to assess clopidogrel response. Nowadays, adenosine diphosphate-induced platelet aggregation (ADP-Ag) remains the gold standard and has been the most widely correlated with clinical events in large sample size studies (7,8). Previous studies from our group and others proposed a threshold value of ADP-Ag >70% to identify clopidogrel nonresponders with higher risk of recurrent ischemic events, including stent thrombosis (ST) (5,8,11). Therefore, with this cut-off value, we conducted a prospective and randomized study to assess the benefit of GP IIb/IIIa inhibitor administration in clopidogrel nonresponders undergoing elective PCI.

Abbreviations and Acronyms

ACS = acute coronary syndrome
ADP-Ag = adenosine diphosphate-induced platelet aggregation
CV = cardiovascular
GP = glycoprotein
PCI = percutaneous coronary intervention
PPP = platelet-poor plasma
PRP = platelet-rich plasma
ST = stent thrombosis
VASP = vasodilator-stimulated phosphoprotein

Methods

Study population. Patients older than 18 years with stable angina or a positive functional study with a planned PCI with stent implantation of a de novo lesion in a native coronary artery were prospectively eligible for inclusion. Exclusion criteria were: left ventricular ejection fraction <30%, acute coronary syndrome in the previous month, prior myocardial infarction in the target vessel related territory, positive biomarkers pre-PCI, platelet count <100 g/l, and history of bleeding diathesis. The study protocol was approved by the institutional ethics committee, and patients gave informed consent for participation. All the patients were receiving chronic aspirin therapy (75 mg daily), and none of them were receiving chronic clopidogrel therapy. Antiplatelet therapy was administered with loading doses of 600 mg of clopidogrel and 250 mg of aspirin the day before the procedure. These loading doses were administrated under control of a nurse to avoid any problem with compliance. After hospital discharge, all the patients identified as nonresponders to clopidogrel received aspirin 75 mg and clopidogrel 150 mg for at least 1 month.

Blood samples and platelet aggregation. Blood samples were drawn the morning before the procedure, at least 12 h after the loading dose of clopidogrel and aspirin. Blood was immediately collected in a vacutainer tube containing 3.8% trisodium citrate, filled to capacity, and sent immediately to the hemostasis laboratory. The blood-citrate mixture was centrifuged at 120 *g* for 5 min. The resulting platelet-rich plasma (PRP) was kept at room temperature for use within 1 h. The platelet count was determined in the PRP sample and adjusted to 2.5×10^8 ml–1 with homologous platelet-poor plasma (PPP). Platelets were stimulated with ADP (10 μmol/l), and aggregation was assessed with a PAP4 Aggregometer (Biodata Corporation, Wellcome, Paris, France). Aggregation was expressed as the maximal percentage change in light transmittance from baseline with PPP as reference. Here we report data on maximal intensity of platelet aggregation with ADP. The coefficient of variation of maximal intensity of platelet aggregation with ADP was 6.5%. The normal ranges obtained from a healthy population are 69% to 104% for ADP-Ag. Nonresponse to clopidogrel was defined by ADP-Ag >70%, as described previously (5,8,11).

Procedure. After assessment of clopidogrel response, clopidogrel nonresponders were randomized 1:1 to the "conventional group" with GP IIb/IIIa antagonists left to the physician's discretion according to current guidelines or the "active group" with systematic administration of GP IIb/IIIa antagonist (Abciximab) (Fig. 1). Patients in the "active" group received abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125-μg/kg/min [maximum, 10 μg/min] infusion for 12 h), plus heparin, 50 U/kg of body weight. Patients in the "conventional" group received heparin bolus, 70 U/kg.

End points. The clinical end point included the following cardiovascular (CV) events during 1-month follow-up: death from any cause, periprocedural myonecrosis, acute or subacute definite or probable ST, and recurrent ACS. Follow-up events were prospectively assessed by clinical visit. Recurrent ACS was defined by the presence of symptoms compatible with recurrent ischemia needing new hospital stay and coronary angiography. Stent thrombosis was defined according to the new Academic Research Consortium definitions. Periprocedural myonecrosis was defined as post-procedural increase of troponin I higher than the upper limit of normal (>0.4 ng/ml). Drug therapy compliance was assessed. Occurrence of major bleeding according to the Thrombolysis In Myocardial Infarction criteria (14) was reported.

Statistical analysis. Statistical analysis was performed with the Graphpad Prism Software (version 4.00, Graphpad Software, Inc., San Diego, California). Continuous variables are ex-

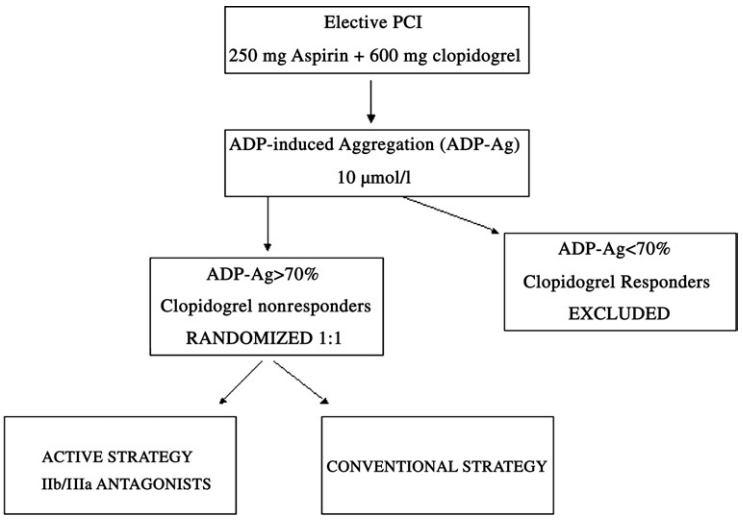

Figure 1. Design of the Study

Patients admitted for elective coronary stenting included if nonresponder to clopidogrel according to adenosine diphosphate-induced platelet aggregation (ADP-Ag) and randomized to either active or conventional strategy. PCI = percutaneous coronary intervention.

pressed as mean ± SD. Categorical variables are expressed as frequencies and percentages. Comparisons between the groups were made with the chi-square or Fisher exact test for categorical variables, and mean levels were compared with the unpaired *t* test for continuous variables. Data were evaluated with an intent-to-treat analysis. We calculated that >130 patients should be included to detect a difference of 50% between both groups (alpha 0.05, beta 0.20, statistical power 0.80). Patient curves for freedom from death or major adverse cardiac events were constructed according to Kaplan and Meier. Comparisons were made with the log-rank test. Statistical significance was set at $p < 0.05$.

Results

Among 643 patients scheduled for planned PCI, 149 clopidogrel nonresponders (23%) (ADP-Ag >70%) were prospectively included and randomized to the "conventional group" (n = 75) or the "active group" (n = 74).

Baseline characteristics of the patients randomized to both strategies were similar (Table 1). Two patients (3%) in the "conventional group" received a GP IIb/IIIa antagonist during the procedure. Procedural data were comparable between groups (Table 2). The mean time between the loading dose and blood sampling was 18.3 ± 2.1 h in the whole population and similar between groups.

Clinical follow-up was performed 1 month after PCI in all patients. The rate of CV events was significantly lower in the "active group" than in the "conventional group": 19% (n = 14) versus 40% (n = 30), p = 0.006; odds ratio: 2.8; 95% confidence interval: 1.4 to 6.0 (Fig. 2). During 1-month follow-up, the CV events were 1 and 0 for death, 1 and 0 for ST, 2 and 1 for recurrent ACS, and 26 and 13 for periprocedural myonecrosis in the "conventional" and "active" groups, respectively (Fig. 3). No patient in either

Table 1. Baseline Characteristics Randomized to "Active" or "Conventional" Strategy

Characteristics	Active Strategy (n = 74)	Conventional Strategy (n = 75)	p Value
Male	55 (74)	58 (77)	0.71
Age (yrs)	66 ± 9	64 ± 8	0.68
Body mass index (kg/m^2)	27 ± 4	28 ± 5	0.82
CV risk factors			
Hypertension	48 (65)	45 (60)	0.61
Diabetes mellitus	26 (35)	30 (40)	0.62
Smoker	22 (30)	26 (49)	0.60
Dyslipidemia	54 (74)	57 (76)	0.71
Familial history	14 (19)	18 (24)	0.55
Discharge medications			
Statins	60 (81)	62 (83)	0.83
Beta blocker	41 (55)	39 (52)	0.74
ACE inhibitors	33 (45)	36 (48)	0.73
Ejection fraction	62 ± 11	60 ± 14	0.59
Biological data			
Creatinine (mg/dl)	97 ± 12	102 ± 21	0.78
CRP (mmol/l)	2.5 ± 0.8	2.7 ± 0.7	0.70
Platelet count	211 ± 33	225 ± 43	0.60
ADP-induced aggregation	78 ± 6	78 ± 7	0.84

Values are mean ± SD for quantitative variables and n (%) for qualitative variables.
ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; CRP = C-reactive protein; CV = cardiovascular.

Table 2. Procedural Characteristics Among Patients Randomized to "Active" or "Conventional" Strategy

Characteristics	Active Strategy (n = 74)	Conventional Strategy (n = 75)	p Value
Reference diameter	2.8 ± 0.5	2.6 ± 0.4	0.47
Minimal lumen diameter	1.0 ± 0.3	1.0 ± 0.2	0.27
% stenosis	64 ± 9	66 ± 10	0.38
Residual stenosis, %	11 ± 3	11 ± 3	0.97
Total stent length, mm	24 ± 9	25 ± 7	0.66
Stent diameter, mm	3 ± 0.3	3 ± 0.4	0.83
GP IIb/IIIa antagonists	74 (100)	2 (3)	<0.0001

Values are mean ± SD for quantitative variables and n (%) for qualitative variables.
GP = glycoprotein.

group had post-procedural Thrombolysis In Myocardial Infarction major bleeding or required transfusions.

Discussion

The present study suggested benefit of tailored antiplatelet therapy during elective PCI with GP IIb/IIIa antagonist for clopidogrel nonresponders.

Numerous biological studies, usually based on ADP-Ag, have reported interindividual variability in platelet response to clopidogrel with clinical relevance (4–8). Recently, a new flow cytometric vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay has been introduced to measure specific inhibition of clopidogrel's biochemical target via the P2Y12 receptor. The platelet reactivity index VASP has been associated with recurrent ischemic events after PCI (9) and after non–ST-segment elevation ACS

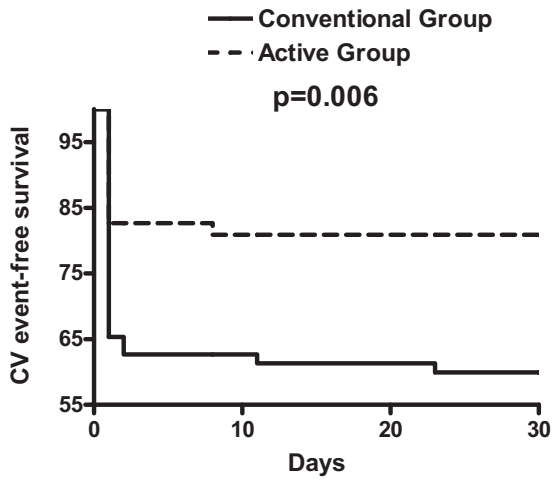

Figure 2. Kaplan-Meier Analysis for 30-Day Clinical Outcome According to Group

Log-rank = 7.5, p = 0.006. CV = cardiovascular.

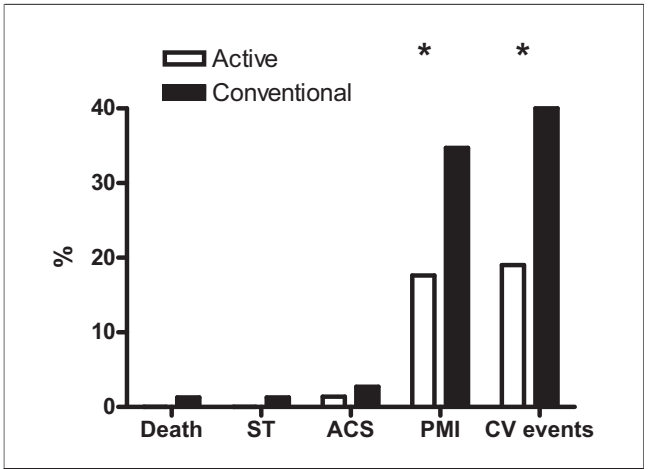

Figure 3. Incidence of CV Events According to the Strategy

*p < 0.01. ACS = acute coronary syndrome; CV = cardiovascular; PMI = periprocedural myonecrosis; ST = stent thrombosis.

(10). The remaining question was to define the strategy to overcome nonresponse to clopidogrel in these high-risk patients. Several strategies have been proposed to improve antithrombotic therapy of these nonresponders. In a well-conducted study, Bonello et al. (9) proposed additional loading doses with repeated VASP assay. This strategy was associated with better clinical outcome but required a longer hospital stay length and deferred PCI. The VASP assay is probably the most specific platelet test to assess P2Y12 pathway inhibition and has been proposed by these authors to adapt antiplatelet therapy. However, the clinical data supporting predictive value of the VASP are lower than ADP-Ag and based on small sample-size single-center studies (9,10). Moreover, the threshold proposed for this test has a good sensitivity and negative predictive value but very poor specificity or positive predictive value (9,10). Indeed, these cutoff values identified up to 80% of nonresponders (10), suggesting a need to adapt medications for more than one-half of the patients referred to PCI. Whether this test is accurate to identify a high-risk subgroup or the cutoff value proposed is discriminative enough will have to be addressed. Before wide use of clopidogrel, GP IIb/IIIa antagonists were used in elective PCI. Recently, the ISAR REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) study suggested that, in patients at low-to-intermediate risk who undergo elective PCI after pre-treatment with a high loading dose of clopidogrel, abciximab was not associated with any clinically measurable benefit at 30 days (15). In contrast, the ISAR REACT 2 study showed that abciximab reduced the risk of adverse events in patients with non–ST-segment elevation ACS with positive troponin undergoing PCI after pre-treatment with 600 mg of clopidogrel (16). The present study identified another subgroup of patients undergoing PCI who

might benefit from periprocedural abciximab administration, the clopidogrel nonresponders.

Our findings underline the necessity to optimize the degree of platelet inhibition at the time of PCI. The development of new ADP-antagonists could be helpful in these clinical settings. Indeed, a multicenter randomized study demonstrated the clinical superiority for ischemic end points but with a significant increased bleeding risk (13). Development of these new drugs with more potent, rapid, and consistent antiplatelet effects might solve the issue of "clopidogrel resistance" and lead us to shift from antiplatelet resistance to bleeding risk assessment.

Adjusted antiplatelet therapy based on platelet testing could be more easily feasible with development of point-of-care platelet assay usable in daily clinical practice. Indeed, ADP-Ag and VASP have been widely used to assess peri-PCI platelet function. However, these laboratory tests require experienced staff, time, and sample preparation. Thus, there is a clinical need to have a reliable assay for measuring platelet function after antiplatelet therapy for monitoring and potentially tailoring antiplatelet dosing regimens to individual patients. The cartridge-based VerifyNow point-of-care platelet function assay (Accumetrics, San Diego, California) was designed to overcome the practical limitations of conventional in vitro laboratory tests of platelet function. This test has been recently associated with recurrent clinical events after elective PCI (17). Whether tailored antiplatelet therapy integrating both ischemic and bleeding risks with this point-of-care assay will improve clinical prognosis has to be addressed in randomized trials.

Study limitations. The sample size of the present study is relatively small and does not allow definitive conclusions. The main difference between groups for clinical events is related to a lower rate of periprocedural myonecrosis and not a hard clinical end point such as death or ST. However, our study included a low-risk population of elective PCI, and periprocedural myonecrosis has been associated with adverse mid- or long-term prognosis including mortality (18).

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