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Aspirin and Clopidogrel Drug Response in Patients Undergoing Percutaneous Coronary Intervention

The Role of Dual Drug Resistance

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OBJECTIVES We sought to evaluate the response to clopidogrel among aspirin-resistant versus aspirin-sensitive patients undergoing percutaneous coronary intervention (PCI).

BACKGROUND Wide variability has been reported in response to aspirin and clopidogrel. There are limited data on the simultaneous responses to both drugs.

METHODS Elective PCI patients (n = 150) who received aspirin for ≥1 week but not clopidogrel were included. All patients received bivalirudin during PCI. Blood samples were drawn at baseline and 20 to 24 h after a 300-mg clopidogrel dose. Aspirin resistance was defined by ≥2 of 3 criteria: rapid platelet function analyzer-ASA score ≥550, 5 μmol/l adenosine diphosphate (ADP)-induced aggregation ≥70%, and 0.5 mg/ml arachidonic acid-induced aggregation ≥20%. Clopidogrel resistance was defined as baseline minus post-treatment aggregation ≤10% in response to 5 and 20 μmol/l ADP.

RESULTS Nineteen (12.7%) patients were resistant to aspirin and 36 (24%) to clopidogrel. Nine (47.4%) of the aspirin-resistant patients were also clopidogrel resistant. Aspirin-resistant patients were more likely to be women and have diabetes than were aspirin-sensitive patients. They also had lower response to clopidogrel, assessed by platelet aggregation and activation markers (flow cytometry-determined PAC-1 binding and P-selectin expression). Elevation of creatine kinase-myocardial band after stenting occurred more frequently in aspirin-resistant versus aspirin-sensitive patients (38.9% vs. 18.3%; p = 0.04) and in clopidogrel-resistant versus clopidogrel-sensitive patients (32.4% vs. 17.3%; p = 0.06).

CONCLUSIONS Aspirin-resistant patients as a group have reduced response to clopidogrel. Furthermore, we have identified a unique group of dual drug-resistant patients who may be at increased risk for thrombotic complications after PCI. (J Am Coll Cardiol 2006;47:27–33) © 2006 by the American College of Cardiology Foundation

Aspirin and clopidogrel have become standard therapy in patients undergoing percutaneous coronary intervention (PCI) with stenting. However, there is considerable heterogeneity in the responses of individual patients to each of these drugs (1–4). Previous studies have estimated that adequate antiplatelet effects are not achieved in 5% to 45% of patients taking aspirin and 4% to 30% of patients taking clopidogrel (1,3–8).

Resistance to the antiplatelet effects of aspirin has been associated with adverse clinical outcomes (2,5) and with an increase in markers of myonecrosis following PCI (9). It has been proposed that aspirin-resistant patients be treated routinely with alternative antiplatelet drugs, mainly clopidogrel. However, it is not clear whether the response to clopidogrel is similar in aspirin-resistant and aspirin-sensitive patients. Platelets from aspirin-resistant patients appear to have increased sensitivity to agonists such as adenosine diphosphate (ADP) and collagen (10,11). Furthermore, aspirin resistance has been associated with platelet hyperreactivity (10,12). These hyperreactive platelets may also be less responsive to inhibition by other antiplatelet drugs such as clopidogrel.

There are limited data regarding the simultaneous responses to both aspirin and clopidogrel. Lepantalo et al. (13) recently reported that among 50 patients undergoing PCI, 5 (10%) were "poor responders" to both aspirin and clopidogrel. Although this study is limited by the small number of patients, it suggests that a subgroup of patients may have low response to both drugs. Our aim, therefore, was to evaluate prospectively the response to clopidogrel among aspirin-resistant versus aspirin-sensitive patients, and to characterize factors that affect the responses to either drug in patients undergoing elective PCI.

METHODS

Patients. We enrolled patients scheduled for elective PCI between November 2003 and February 2005. All patients had received aspirin 81 to 325 mg daily for ≥1 week before PCI and had not received a thienopyridine or glycoprotein (GP) IIb/IIIa inhibitor in the week prior to enrollment. Patients were enrolled if they were planned to receive

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Abbreviations and Acronyms

AA	= arachidonic acid
ADP	= adenosine diphosphate
ARU	= aspirin reaction units
CK-MB	= creatine kinase-myocardial band
GP	= glycoprotein
MFI	= mean fluorescence intensity
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
RPFA-ASA	= rapid platelet function assay-aspirin

bivalirudin rather than heparin and a GP IIb/IIIa inhibitor during PCI, because bivalirudin does not affect ADP-induced platelet aggregation (14). Exclusion criteria were acute myocardial infarction (MI) within one week, any contraindications to aspirin, clopidogrel, or bivalirudin, thrombocytopenia ($<100 \times 10^3$ cells/mm^3), anemia (hemoglobin <10 g/dl), or renal failure (creatinine >2.5 mg/dl).

This study was approved by the Investigational Review Board of the Baylor College of Medicine; all patients gave informed consent. Our aim was to enroll 150 patients. One hundred sixty patients were initially enrolled. Ten patients receiving GP IIb/IIIa inhibitors during PCI were withdrawn from the study, leaving 150. All patients underwent coronary stent implantation.

Medications. Immediately following PCI all patients received 300 mg clopidogrel and 325 mg oral aspirin in the catheterization laboratory under direct supervision, followed by 75 mg clopidogrel and 325 mg aspirin daily thereafter. During PCI all patients received a standard course of intravenous bivalirudin bolus 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h until PCI completion.

Blood sampling. Two blood samples were collected in tubes containing 3.2% citrate. The tubes were filled to capacity and then gently mixed. The first (baseline) blood sample was obtained in the catheterization laboratory, prior to PCI and clopidogrel loading, from a 6- to 7-F arterial sheath. The second sample was obtained from an antecubital vein, using a 21-gauge needle, 20 to 24 h after PCI. Blood samples were processed within 1 h of collection.

Platelet aggregation. Turbidimetric platelet aggregation was performed in platelet-rich plasma with a platelet count adjusted to 250×10^3/mm^3. Platelets were stimulated with 0.5 mg/ml (1.6 mmol/l) arachidonic acid (AA) and with 5 and 20 μmol/l ADP. Aggregation was performed with a BioData PAP-4 platelet aggregometer (BioData, Horsham, Pennsylvania). The extent of aggregation was defined as the maximal light transmission ≤6 min after addition of the agonist, with platelet-poor plasma used as reference.

Platelet activation. Platelet activation was determined by assessing platelet surface expression of activated GP IIb/IIIa receptors and P-selectin in response to ADP stimulation, using flow cytometry as previously described (15). Briefly, GP IIb/IIIa activation was assessed using a fluorescein isothiocyanate-conjugated PAC-1 antibody (Becton Dickinson, San Jose, California), and P-selectin expression was determined using an R-phycoerythrin-conjugated anti-CD62P antibody (BD Pharmingen, San Jose, California). Citrated whole blood was diluted with Tyrode's buffer and stimulated for 5 min with 10 μmol/l ADP (final concentration). After adding the corresponding antibody and incubating for 20 min, the mixture was fixated with phosphate-buffered saline containing 1% paraformaldehyde. Samples were analyzed with a Coulter Epics XL MCL flow cytometer (Beckman-Coulter, Miami, Florida). Non-stimulated samples served as negative controls. Both PAC-1 binding and P-selectin were expressed as log mean fluorescence intensity (MFI) and as percentage change in MFI from baseline to the post-PCI sample.

Rapid platelet function assay-aspirin (RPFA-ASA). A point-of-care system (VerifyNow; Accumetrics, San Diego, California), that uses cartridges containing fibrinogen-coated beads and platelet agonists, RPFA-ASA measures platelet agglutination in response to metallic cations and propyl gallate, which activate the cyclooxygenase-1 pathway. (The RPFA-ASA system we used differs from the currently available assay, which employs AA as the agonist.) Results are expressed as aspirin reaction units (ARU). An ARU ≥550 indicates that aspirin-induced platelet dysfunction has not been detected (9).

Markers of myonecrosis. Creatine kinase-myocardial band (CK-MB) levels were measured from frozen plasma samples taken 20 to 24 h after PCI, using a sandwich immunoassay (Advia Centaur CKMB assay; Bayer HealthCare, Tarrytown, New York). Creatine-MB levels were available for 144 patients. In all patients who had elevated levels of CK-MB after PCI, normal CK-MB levels at baseline were confirmed using the same assay. The upper limit of normal for CK-MB is 5.0 ng/ml.

Definitions. Clopidogrel resistance was defined as an absolute difference between baseline and post-treatment aggregation ≤10% in response to both 5 and 20 μmol/l ADP (3,8). High post-clopidogrel platelet aggregation was defined as >75th percentile aggregation in response to 5 and 20 μmol/l ADP (16). The definition of aspirin resistance has been less uniform (17). We employed a primary definition that incorporated previously used criteria (5,6,9) and required the presence of at least two of the following three: 1) 0.5 mg/ml AA-induced platelet aggregation ≥20%; 2) 5 μmol/l ADP-induced platelet aggregation ≥70%; and 3) RPFA-ASA ARU ≥550. To enable comparison with previous studies, alternate analyses of the association between aspirin and clopidogrel response were performed using two additional definitions: 1) criteria 1 + 2 (5); and 2) criterion 3 (9). Aspirin resistance was determined using the baseline blood samples.

Sample size and statistical analysis. The sample size was predetermined based on logistic regression power analysis with a clopidogrel resistance rate of 30% used as the end point (3). Logistic regression of response to clopidogrel with

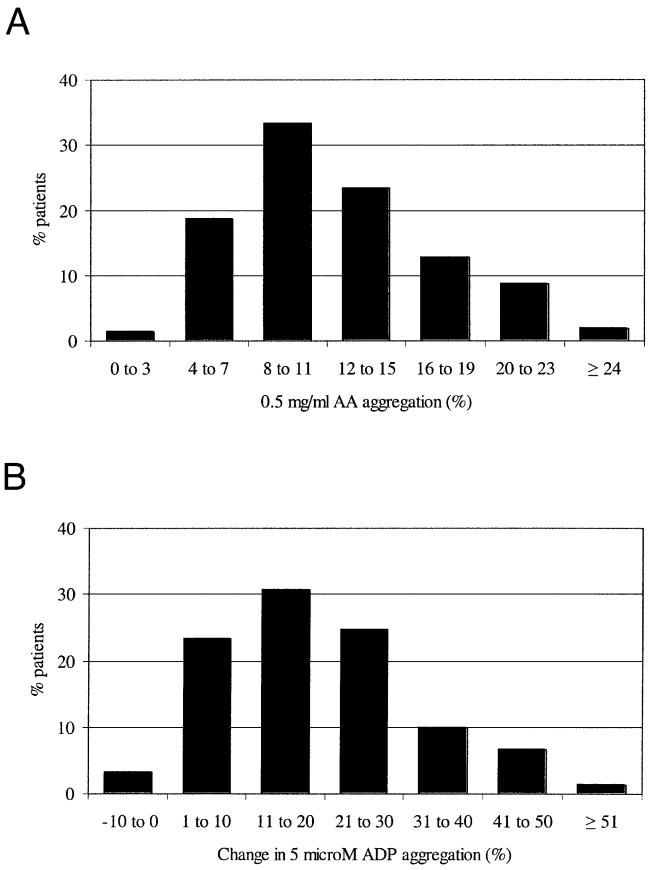

Figure 1. Distribution of the response to **(A)** aspirin (assessed by 0.5 mg/ml arachidonic acid [AA]-induced platelet aggregation) and **(B)** clopidogrel (evaluated by change in 5 μmol/l adenosine diphosphate [ADP]-induced aggregation) from baseline to post-treatment. Both distributions were normal ($p = 0.0003$ and $p = 0.01$, respectively).

a sample size of 150 observations achieves 80% power at 0.05 significance level to detect a change of 20% between the two study groups (aspirin resistant vs. aspirin sensitive).

Continuous variables are presented as mean values ± SD. Comparisons between continuous variables were performed using unpaired Student *t* tests, because they were normally distributed (demonstrated by the Shapiro-Wilk test) (Fig. 1). Comparisons between categorical variables were performed using Fisher exact tests if any subgroups consisted of five or fewer items; otherwise, chi-square tests were used. The response to clopidogrel, expressed as change in platelet aggregation or activation markers from baseline to post-treatment, was compared among aspirin-resistant versus sensitive patients using unpaired Student *t* tests. Two further analyses were performed. The response to clopidogrel was compared among tertiles of AA-induced aggregation using analysis of variance (ANOVA). In addition, the percentages of patients with high post-clopidogrel aggregation were compared with aspirin-resistant versus aspirin-sensitive patients. Analyses were performed using SPSS version 11 statistical software (SPSS Inc., Chicago, Illinois); statistical significance was set at $p < 0.05$.

RESULTS

Clopidogrel and aspirin resistance rates. Thirty-six patients (24%) met the definition of clopidogrel resistance. Aspirin resistance was observed in 19 patients (12.7%) using the primary definition (≥2 of the three criteria), 14 patients (9.3%) using the definition of AA-induced aggregation ≥20% and 5 μmol/l ADP-induced aggregation ≥70%, and 23 patients (15.3%) with the definition of RPFA-ASA ARU ≥550 (Table 1). Regardless of which aspirin resistance definition was used, about 50% of patients who were aspirin resistant were also resistant to clopidogrel, and about 20% of aspirin-sensitive patients were clopidogrel resistant ($p \leq 0.02$) (Table 1). All subsequent comparisons between aspirin-resistant and aspirin-sensitive patients were performed using the primary definition.

To assess the role of prior medication compliance on aspirin resistance we compared AA-induced aggregation before and 20 to 24 h after the witnessed dose of aspirin. There were no significant differences in AA-induced aggregation between the two time points among aspirin-resistant patients (pre-PCI 20.2 ± 4.5% vs. post-PCI 18.8 ± 2.9%; $p = 0.2$) or among aspirin-sensitive patients (pre-PCI 10.5 ± 4.7% vs. post-PCI 10 ± 3.7%; $p = 0.3$).

Patient and procedural characteristics. Compared with aspirin-sensitive patients, aspirin-resistant patients were more likely to be women and to have diabetes (Table 2). Of the 47 women, 11 (23.4%) were aspirin resistant compared with only 8 (7.8%) of the 103 men ($p = 0.01$). Aspirin-resistant patients also had lower hemoglobin levels than aspirin-sensitive patients. There were no differences in patient characteristics between clopidogrel-resistant and clopidogrel-sensitive patients (Table 2). We also compared the characteristics of dual drug-resistant patients (resistant to both aspirin and clopidogrel; $n = 9$) to those of dual

Table 1. Rates of Clopidogrel Resistance in Aspirin-Resistant Versus Aspirin-Sensitive Patients

Aspirin Resistance Definition	ASA-Resistant Patients (n)	Clopidogrel Resistance Among ASA-Resistant Patients	ASA-Sensitive Patients (n)	Clopidogrel Resistance Among ASA-Sensitive Patients	p Value
At least 2 of the 3 criteria	19	9 (47.4%)	131	27 (20.6%)	0.01
AA aggregation ≥20% and ADP aggregation ≥70%*	14	7 (50%)	136	29 (21.3%)	0.02
RPFA-ASA ARU ≥550	23	11 (47.8%)	127	25 (19.7%)	0.01

*0.5 mg/ml arachidonic acid-induced aggregation ≥20% and 5 μmol/l ADP–induced aggregation ≥70%.
ADP = adenosine diphosphate; ASA = aspirin; RPFA-ASA ARU = rapid platelet function assay-ASA expressed in aspirin reaction units.

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Table 2. Baseline Clinical Characteristics, Laboratory Data, and Medications

	Aspirin Resistant (n = 19)	Aspirin Sensitive (n = 131)	Clopidogrel Resistant (n = 36)	Clopidogrel Sensitive (n = 114)
Age (yrs)	67.2 ± 10.6	65.3 ± 10.6	64.3 ± 10.1	65.9 ± 11.3
Women	11 (57.9%)*	36 (27.5%)*	15 (41.7%)	32 (28.1%)
BMI (kg/m^2)	30.9 ± 7.2	29.8 ± 5	31.3 ± 6	29.4 ± 5
Diabetes	10 (52.6%)†	38 (29%)†	12 (33.3%)	36 (31.6%)
Hypertension	16 (84.2%)	110 (84%)	30 (83.3%)	96 (84.2%)
Hyperlipidemia	16 (84.2%)	91 (69.5%)	26 (72.2%)	81 (71.1%)
Smoking	7 (36.8%)	42 (32.1%)	11 (30.6%)	38 (33.3%)
Prior MI	3 (15.8%)	26 (19.8%)	9 (25%)	20 (17.5%)
Prior CABG	3 (15.8%)	28 (21.4%)	8 (22.2%)	23 (20.2%)
Laboratory data				
Hemoglobin (g/dl)	12.7 ± 1.3*	13.9 ± 1.6*	13.6 ± 1.8	13.8 ± 1.5
WBC (10^3/mm^3)	8.7 ± 2.6	7.4 ± 2.4	8.2 ± 2.5	7.3 ± 2.4
Platelets (10^3/mm^3)	236.9 ± 71	204.8 ± 62	218.4 ± 64	204.9 ± 62.8
Mean platelet volume (fl)	9.8 ± 1.6	9.4 ± 1.2	9.9 ± 1.5	9.3 ± 1.4
Creatinine (mg/dl)	1.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3
Baseline medications				
Aspirin 81 mg	10 (52.6%)	50 (38.2%)	15 (41.7%)	45 (39.5%)
Aspirin 325 mg	9 (47.4%)	81 (61.8%)	21 (58.3%)	69 (60.5%)
Statins	16 (84.2%)	92 (70.2%)	28 (77.8%)	80 (70.2%)
Beta-blockers	14 (73.7%)	72 (55%)	25 (69.4%)	61 (53.5%)
ACEI/ARB	6 (31.6%)	50 (38.2%)	9 (25%)	47 (41.2%)
CCB	3 (15.8%)	26 (19.8%)	5 (13.9%)	24 (21.1%)

*$p \leq 0.01$; †$p \leq 0.05$; for aspirin resistance vs. aspirin sensitivity.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; CABG = coronary artery bypass graft; CCB = calcium channel blockers; MI = myocardial infarction; Smoking = current or former; WBC = white blood cells.

drug-sensitive patients (n = 104). Dual drug-resistant patients were more likely to be women (67.7% vs. 26.9%; p = 0.02) and had higher mean body mass index (33.8 ± 7.9 kg/m^2 vs. 29.7 ± 5 kg/m^2; p = 0.03). Among the whole study cohort, 60 (40%) patients were treated with 81 mg aspirin at the time of enrollment and 90 (60%) were treated with 325 mg. Ten (16.7%) of the 60 patients receiving 81 mg were aspirin resistant, compared with 9 (10%) of the 90 patients receiving 325 mg (p = 0.25).

There were no differences in indications for the PCI or procedural characteristics between aspirin-resistant and aspirin-sensitive patients or between clopidogrel-resistant and clopidogrel-sensitive patients (Table 3).

Response to clopidogrel among aspirin-resistant versus -sensitive patients. Aspirin-resistant patients had a significantly lower degree of reduction of platelet aggregation in response to 5 and 20 μmol/l ADP after clopidogrel (Table 4). They also displayed less inhibition of PAC-1 binding and a lower degree of reduction in P-selectin expression after clopidogrel treatment (Table 4).

The percentage of patients with high post-clopidogrel ADP-induced aggregation (>75th percentile) was higher among aspirin-resistant than aspirin-sensitive patients (5 μmol/l ADP: 78.9% vs. 18.3%, p = 0.001; 20 μmol/l ADP: 73.4% vs. 19.1%, p = 0.001). Furthermore, comparison of the change in ADP-induced aggregation among tertiles

Table 3. Indications for Percutaneous Coronary Intervention and Procedural Characteristics

	Aspirin Resistant (n = 19)	Aspirin Sensitive (n = 131)	Clopidogrel Resistant (n = 36)	Clopidogrel Sensitive (n = 114)
Indication				
Stable angina	10 (52.6%)	55 (42%)	19 (52.8%)	46 (40.4%)
Unstable angina	4 (21.1%)	34 (26%)	8 (22.2%)	30 (26.3%)
NSTEMI >1 week	3 (15.8%)	11 (8.4%)	2 (5.6%)	12 (10.5%)
(+) Stress test	4 (21.1%)	46 (35.7%)	12 (33.3%)	38 (33.3%)
Procedural characteristics				
Total stent length (mm)	22.6 ± 9.3	21.2 ± 9.9	23.5 ± 11	20.7 ± 9.4
Minimal stent diameter (mm)	3.0 ± 0.6	3.0 ± 0.4	3.0 ± 0.5	3.0 ± 0.4
No. of stents/patient	1.4 ± 0.6	1.3 ± 0.6	1.5 ± 0.7	1.3 ± 0.5
Drug-eluting stents	15 (78.9%)	117 (89.3%)	31 (86.1%)	100 (87.7%)
Bare-metal stents	4 (21.1%)	14 (10.7%)	5 (13.9%)	14 (12.3%)

NSTEMI = non–ST-segment elevation myocardial infarction; (+) Stress test = positive stress test.

Table 4. Response to Clopidogrel Among Aspirin-Resistant Versus Aspirin-Sensitive Patients

	Aspirin Resistant (n = 19)	Aspirin Sensitive (n = 131)	p Value
Absolute change in 20 μmol/l ADP aggregation (%)	8.3 ± 7.3	15.0 ± 10.2	0.001
Absolute change in 5 μmol/l ADP aggregation (%)	13.8 ± 9.7	20.6 ± 12.5	0.01
Absolute change in PAC-1 binding (MFI)	0.8 ± 1.5	1.7 ± 1.2	0.01
Absolute change in P-selectin expression (MFI)	4.1 ± 3.4	5.6 ± 3.5	0.09
Relative change in PAC-1 binding (%)	14.6 ± 25.6	35 ± 24.1	0.002
Relative change in P-selectin expression (%)	25.9 ± 23.8	40.4 ± 21.8	0.02

Absolute change = absolute difference between baseline and post-treatment aggregation; relative change = percentage decrease from baseline.
ADP = adenosine diphosphate; MFI = mean fluorescence intensity.

of AA-induced aggregation revealed a significant difference between the tertiles (5 μmol/l ADP, p = 0.006; 20 μmol/l ADP, p = 0.0001) (Fig. 2). Patients in the highest tertile (reflecting lower response to aspirin) had the least reduction in ADP-induced aggregation after clopidogrel treatment.

Comparison of baseline platelet reactivity showed a trend toward higher baseline P-selectin levels among aspirin-resistant versus aspirin-sensitive patients (15.6 ± 5.1 MFI vs. 13.8 ± 4.2 MFI; p = 0.1).

Markers of myonecrosis. Levels of CK-MB post-PCI were available for 144 patients. Thirty (20.8%) of the 144 patients had CK-MB levels above the upper limit of normal (Fig. 3). Elevation of CK-MB occurred more frequently in aspirin-resistant than in aspirin-sensitive patients (38.9% vs. 18.3%; p = 0.04) and in dual drug-resistant than in dual drug-sensitive patients (44.4% vs. 15.8%; p = 0.05). There was also a trend toward more frequent CK-MB elevations among clopidogrel-resistant versus clopidogrel-sensitive patients (32.4% vs. 17.3%; p = 0.06).

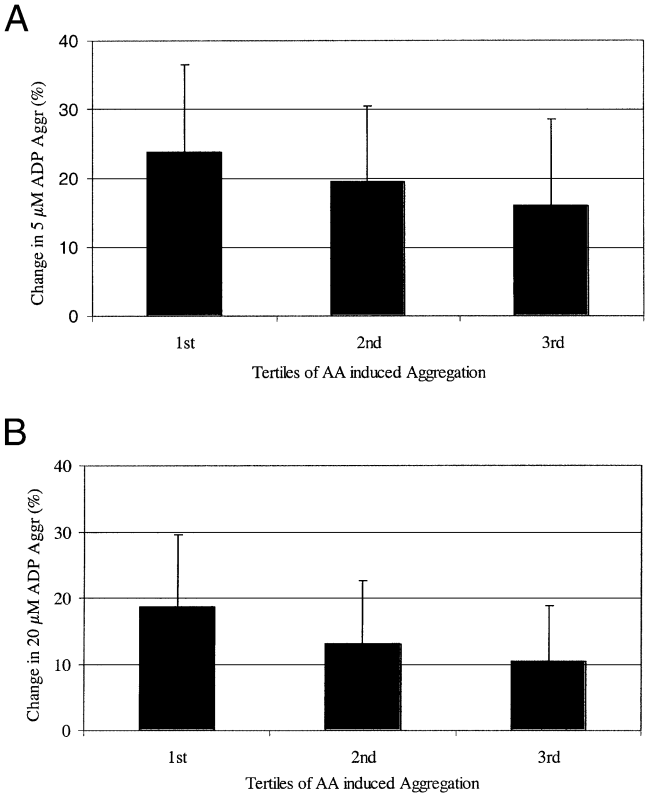

Figure 2. Response to clopidogrel among the three tertiles of 0.5 mg/ml arachidonic acid (AA)-induced aggregation (reflecting response to aspirin). Aggregation in response to **(A)** 5 μmol/l and **(B)** 20 μmol/l adenosine diphosphate (ADP) (p = 0.006 and p = 0.0001, respectively, for difference between tertiles).

DISCUSSION

This is the first study to characterize the response to clopidogrel among aspirin-resistant compared with aspirin-sensitive patients. It is also the first study of antiplatelet drug response to be performed in the presence of a direct thrombin inhibitor rather than unfractionated heparin, in order to avoid the confounding effects of heparin on platelet activity. We observed aspirin resistance in 9% to 15% of patients, depending on the definition used, and clopidogrel resistance in 24%. About one-half of the aspirin-resistant patients were also resistant to the effects of clopidogrel. Furthermore, we have shown that aspirin-resistant patients as a group display a lower inhibitory response to clopidogrel than aspirin-sensitive patients.

Clinical factors associated with drug resistance. Our secondary objective was to identify clinical factors associated with low response to aspirin or clopidogrel. Aspirin-resistant and dual drug-resistant patients were more likely to be women compared with aspirin-sensitive and dual drug-sensitive patients. This finding is in accordance with the studies of Gum et al. (5) and Chen et al. (9), who also found a higher proportion of women among aspirin-resistant

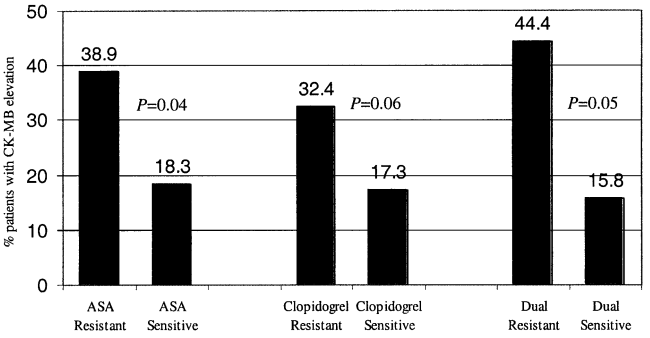

Figure 3. Incidence of creatinine kinase-myocardial band (CK-MB) elevation above the upper limit of normal in aspirin (ASA)-resistant versus aspirin-sensitive patients, clopidogrel-resistant versus clopidogrel-sensitive patients, and dual drug-resistant versus dual drug-sensitive patients.

patients. The greater proportion of women may explain the lower hemoglobin level we observed among aspirin-resistant compared with aspirin-sensitive patients. The consistently higher rates of aspirin resistance among women may also account in part for the recently reported failure of aspirin to reduce the risk of a first MI in women, in contrast to its beneficial primary prevention effects in men (18).

An additional clinical factor we found to be associated with aspirin resistance is diabetes. Platelets from individuals with type 2 diabetes have been shown to have a reduced response to aspirin (19). Furthermore, obesity and insulin resistance have been associated with impaired platelet-inhibitory effects of aspirin in non-diabetic patients (20). This association may explain the significantly elevated BMI we observed in the dual drug-resistant group in our study. Lepantalo et al. (13) reported that low response to clopidogrel was associated with high levels of glycosylated hemoglobin and C-peptide. Therefore, insulin resistance may be associated with reduced response to both drugs.

Possible mechanisms for dual drug resistance. There are several plausible explanations for our findings of lower response to clopidogrel among aspirin-resistant patients as a group. The most likely mechanism is a global increase in platelet reactivity. Platelets from aspirin-resistant patients appear to have increased sensitivity to ADP-induced GP IIb/IIIa activation (10) as well as to low concentrations of collagen (11). Furthermore, patients with diabetes, who comprised more than half of the aspirin-resistant group, have been shown to have a higher proportion of platelets expressing P-selectin and activated GP IIb/IIIa receptors than non-diabetic patients (21,22). Although we observed only a trend toward higher baseline P-selectin expression in aspirin-resistant patients, if indeed these patients have hyper-reactive platelets they may be less sensitive to inhibition by clopidogrel.

Two other mechanisms are also possible. First, increased platelet turnover in aspirin-resistant patients may lead to the release of young platelets still able to form thromboxane A2 through non-cyclooxygenase-1–dependent pathways and respond to ADP despite aspirin and clopidogrel treatment. We did not, however, observe differences in the mean platelet volume, which may reflect platelet age, between the different groups in our study. Second is poor compliance. This is unlikely, however, because the clopidogrel loading dose as well as an aspirin dose were administered in the catheterization laboratory under direct supervision. The second blood sample was drawn 20 to 24 h after this treatment, and there were no differences in AA-induced platelet aggregation between the baseline and post-treatment samples.

Clinical importance. Our study extends previous findings of an association between adverse clinical events and resistance to aspirin (2,5,9) or clopidogrel (23). We evaluated the incidence of CK-MB elevation following PCI, which has been consistently shown to be associated with higher risk of death, MI, and repeat revascularization (24). In accordance with the report by Chen et al. (9), we have found that aspirin-resistant patients had a more than two-fold increase in the incidence of myonecrosis following PCI. Clopidogrel-resistant patients also tended to have more frequent CK-MB elevation compared with clopidogrel-sensitive patients, confirming recent clinical reports (23). Dual drug-resistant patients also had a more than two-fold increase in the rate of myonecrosis compared with dual drug-sensitive patients. This finding supports the recent case-control observation by Wenaweser et al. (25) that among 23 patients with previous stent thrombosis, about half were resistant to the effects of both aspirin and clopidogrel. Taken together, these findings should raise a note of caution that a modest proportion of patients undergoing high-risk PCI may not have adequate antithrombotic protection despite dual antiplatelet therapy.

Study limitations. Our study has several limitations. First, it was powered to evaluate differences in the response to clopidogrel among aspirin-resistant versus aspirin-sensitive patients. However, the sample size was inadequate to estimate the risk of myonecrosis associated with dual drug resistance. Second, the antiplatelet effects of aspirin and clopidogrel were evaluated at two points during a single 24-h period and may not reflect possible temporal fluctuations in individual responses. Nevertheless, these measurements reflect the extent of platelet inhibition just before and following PCI, when optimal inhibition is required. Third, the first blood sample was drawn from an arterial access and the second from a venous access. These conditions were, however, identical for both groups tested. Finally, our study was performed with a clopidogrel loading dose of 300 mg. Recent studies have indicated that a loading dose of 600 mg provides a more rapid and pronounced early response and reduces the rate of clopidogrel resistance (16,26,27). However, most clinical efficacy data have been accrued with the 300 mg dose, and this is the only dose that is currently approved by the U.S. Food and Drug Administration (28).

Conclusions. We have identified a unique group of dual drug-resistant patients who do not achieve adequate antiplatelet effects from either aspirin or clopidogrel. The relatively high incidence of CK-MB elevation after PCI in these patients suggests that they may be at high risk for thrombotic complications following coronary intervention. This finding should be confirmed in a larger-scale study. Nevertheless, the lower response to clopidogrel among aspirin-resistant patients is of particular clinical importance, because clopidogrel has been suggested as alternative therapy for aspirin-resistant patients. Our data would imply that this approach may not be sufficient and that other platelet inhibitors acting on additional targets (other than cyclooxygenase-1 and P2Y12) should be developed and investigated.

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