

## Variability in Platelet Responsiveness to Clopidogrel Among 544 Individuals

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<b>OBJECTIVES</b>	We sought to describe the responses of patients to clopidogrel using ex vivo measures of platelet aggregation and activation in a large, heterogeneous population.
<b>BACKGROUND</b>	Recently, a number of reports, using various definitions, have dichotomized patients who are treated with clopidogrel into a minority of “non-responders” and a majority of “responders.” Such classifications imply that treatment leads to an all-or-none response, with potentially important clinical implications.
<b>METHODS</b>	We conducted secondary post-hoc analyses of a dataset consisting of volunteers (n = 94) and patients after coronary stenting (n = 405), with heart failure (n = 25), and after stroke (n = 20).
<b>RESULTS</b>	The response of subjects to clopidogrel followed a normal, bell-shaped distribution, with a mean and standard deviation of $41.9 \pm 20.8\%$ when aggregation was induced by $5 \mu\text{mol/l}$ of adenosine diphosphate. When hyporesponsiveness and hyper-responsiveness to clopidogrel were considered to be two standard deviations less than and greater than the mean, respectively, the prevalence of hyporesponsiveness and hyper-responsiveness in these patients was 4.2% and 4.8%, respectively. Pretreatment platelet activity and clinical characteristics were not associated with responsiveness to clopidogrel.
<b>CONCLUSIONS</b>	Individuals receiving clopidogrel exhibit a wide variability in response that follows a normal distribution. The clinical implications of this variability are unknown but potentially are important. Clinical trials are needed to define whether hyporesponders to clopidogrel are at increased risk for thrombotic events and whether hyper-responders are at increased risk for bleeding. If so, the individualization of antiplatelet therapy, including clopidogrel dosing, may be possible in the future but will require the ability to easily and reproducibly measure responsiveness by a method that has been proven to be predictive of clinical events. (J Am Coll Cardiol 2005;45:246–51) © 2005 by the American College of Cardiology Foundation

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Variability among patients in the measured response to treatment with an antiplatelet agent has been recognized since 1966 (1). Since that time, numerous small studies have suggested a correlation between clinical outcomes and ex vivo aspirin “non-responsiveness” or “resistance” (2,3), but such a relationship has yet to be proven in adequately powered, large-scale, prospective clinical trials. More recently, a number of reports have been published identifying variability in the level of platelet inhibition achieved with the administration of clopidogrel, with a minority of individuals again being classified as “non-responders” or “resistant” (4–6). Like the studies of aspirin that preceded them, these studies are relatively small and use different platelet assessments and definitions for determining responsiveness.

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Defining patients as either “responsive” or “unresponsive” to an antiplatelet therapy suggests a dichotomous response that is quite different from what is expected and clinically observed in nearly all other therapeutic interventions. Multiple genetic and environmental influences have been shown to affect ex vivo platelet responsiveness in humans, in vivo thrombosis in animal models, and responsiveness to antiplatelet therapies (7–9). Therefore, like other biologic systems under polygenetic and environmental influence, platelet function and response to antiplatelet therapy would be expected to demonstrate a wide range in responses among subjects.

To better understand the interindividual variation in response to clopidogrel therapy, we analyzed a combined database (n = 544) of studies conducted in the Baltimore metropolitan area (1998 to 2004), which we believe makes up the largest clinical data set of clopidogrel-treated subjects in which platelet function has been assessed serially.

### METHODS

**Population (general inclusion and exclusion criteria).** Five hundred forty-four subjects who had been treated with clopidogrel or with aspirin and clopidogrel were eligible for

**Abbreviations and Acronyms**

ADP = adenosine diphosphate  
PRP = platelet-rich plasma

this analysis. To be included in the present analyses, all patients had a baseline sample (before treatment with clopidogrel) and at least one additional sample with evaluable platelet data after treatment with clopidogrel. Volunteers and patients were excluded if they had any clinical issues that could influence measured platelet response. We assessed patient compliance to the study by interview and by pill counting. To reflect an individual's full response to clopidogrel, only those patients whose platelet function tests were performed at least 3 to 4 h or longer after a 300-mg loading dose or, in those not receiving a loading dose, 5 days or longer were included in this analysis. The four cohorts of individuals included in the current analysis are subsequently listed.

**HUMAN VOLUNTEERS WITH MULTIPLE RISK FACTORS OR DOCUMENTED VASCULAR DISEASE (n = 94).** Subjects were eligible for this study if they met all of the following inclusion criteria: a documented history of vascular disease or multiple risk factors for vascular disease. All subjects were free of aspirin upon beginning the study and received 75 mg of clopidogrel immediately after the baseline sample followed by 75 mg once daily thereafter for seven days, at which time platelets were assessed.

**PATIENTS UNDERGOING CORONARY STENTING (n = 405).** All patients had received 325 mg of aspirin daily for at least one week. Most patients (94%) also received a 300-mg clopidogrel-loading dose immediately before intervention, followed by 75 mg of clopidogrel once daily for at least 30 days. Platelet function was assessed at multiple time points in different patients: at baseline, 2 h, 3 h, 4 h, 24 h, 5 days, and 30 days after a loading dose. Because 2 h is not sufficient

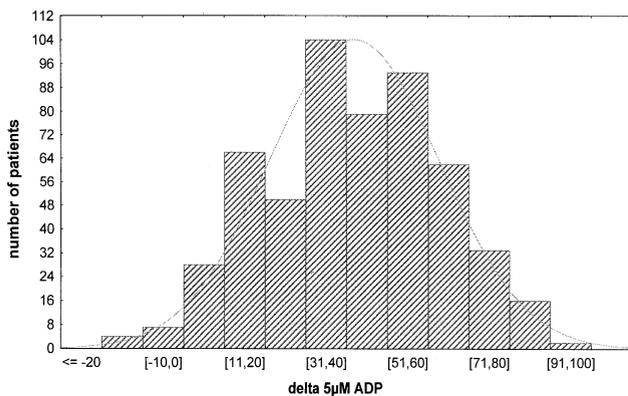
for clopidogrel to exhibit its full antiplatelet efficacy, we used the next evaluable sample (4 to 24 h) in the present analyses.

**PATIENTS WITH HEART FAILURE (n = 25).** Eighty-eight outpatients with a left ventricular ejection fraction <40% or New York Heart Association functional class II to IV congestive heart failure symptoms in the setting of preserved systolic function (10) were included. Only patients who were found to have increased platelet activation at baseline and who were treated with both clopidogrel 75 mg and aspirin 325 mg (n = 25) were included in the current analysis. Platelet function was assessed at baseline and at 30 days after randomization.

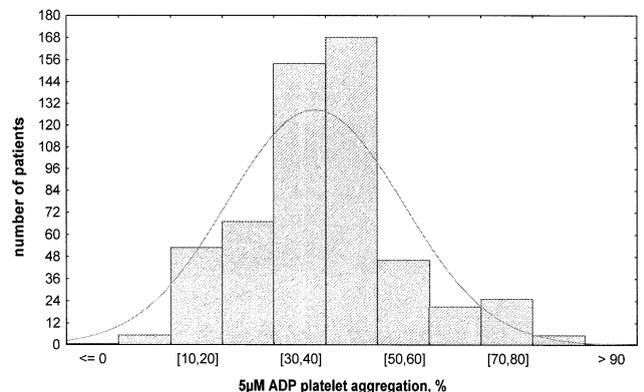
**POST-STROKE PATIENTS OR PATIENTS WITH TRANSIENT ISCHEMIC ATTACK (n = 20).** Patients age  $\geq 40$  years were eligible if they had suffered from ischemic stroke between two and six months earlier and were receiving aspirin (81 mg/day). Twenty patients who were assigned to clopidogrel 75 mg and aspirin 81 mg daily for 30 days were included in the current analysis. Platelet activity was measured at baseline and at 30 days after randomization.

**Samples.** Blood samples were obtained with a 19-gauge needle by direct venipuncture and drawn into 7-ml Vacutainer tubes at room temperature containing 3.8% trisodium citrate. All samples were labeled with a coded number and analyzed by blinded technicians. Research coordinators were not aware of the platelet data, and laboratory personnel did not know the treatment allocation. Platelet studies were performed at baseline and at prespecified time points as noted previously in this work.

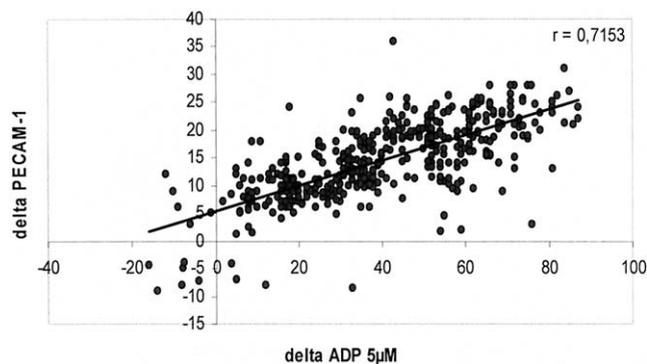
**Platelet assessment. CONVENTIONAL OPTICAL PLATELET AGGREGOMETRY.** The blood-citrate mixture was centrifuged at 1,200 g for 2.5 min. The resulting platelet-rich plasma (PRP) was kept at room temperature for use within 1 h. The platelet count was determined in the PRP sample and adjusted to  $3.5 \times 10^8$ /ml with homologous platelet-poor plasma. Platelets were stimulated with 5  $\mu$ mol of adenosine diphosphate (ADP), and aggregation was assessed using a Chronolog Lumi-Aggregometer (model 560-



**Figure 1.** Distribution of changes in 5  $\mu$ mol of adenosine diphosphate (ADP)-induced platelet aggregation in 544 patients after receiving clopidogrel therapy. Negative changes in aggregation values represent aggregation values after the administration of clopidogrel that were higher than the baseline readings.



**Figure 2.** Distribution of 5  $\mu$ mol of adenosine diphosphate (ADP)-induced residual platelet aggregation in 544 patients after receiving clopidogrel therapy.



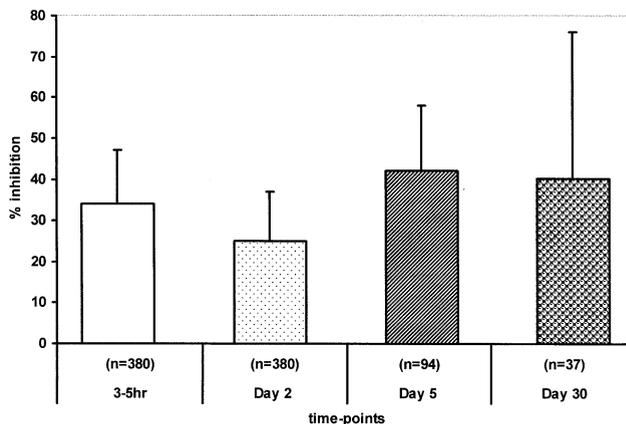
**Figure 3.** Correlation between inhibition of platelet activation as determined by the change in platelet/endothelial cell adhesion molecule-1 (PECAM-1) expression and the change in 5  $\mu$ mol of adenosine diphosphate (ADP)-induced platelet aggregation after treatment with clopidogrel. Negative values resulted from the higher readings after treatment when compared with the baseline measures.

Ca; Chronolog Corp., Haverton, Pennsylvania) with the AggroLink software package (Chronolog Corp.).

**FLOW CYTOMETRY.** The following monoclonal antibodies were used in at least one of the four patient cohorts included in the current analysis: CD41 antigen (glycoprotein IIb) and CD62P (P-selectin; DAKO Corp., Carpinteria, California) and PAC1 (activated glycoprotein IIb/IIIa), CD31 (platelet/endothelial cell adhesion molecule-1), and CD51/CD61 (integrin  $\alpha_v\beta_3$ , vitronectin receptor; PharMingen, San Diego, California). The formation of platelet-leukocyte aggregates was assessed by dual labeling with pan-platelet marker (CD151) and then with CD14, the macrophage receptor for endotoxin lipopolysaccharides. The samples were analyzed on a Becton Dickinson FACScan flow cytometer (Becton Dickinson, San Diego, California) set up to measure fluorescent light scatter as previously described. P selectin was expressed as percent positive cells. Other antigens were expressed as *log* mean fluorescence intensity.

**Definition of clopidogrel response.** Platelet response to clopidogrel was defined as hyporesponders (two standard deviations below the mean), hyper-responders (two standard deviations above the mean), and the rest individuals were defined as standard responders.

**Statistical analysis.** Categorical data are displayed as frequencies and percentages. The chi-square test was used for dichotomous analyses of categorical data. Continuous data are presented as mean values  $\pm$  SD and were compared using one-way repeated measures analysis of variance. Normal distribution of the data was tested with Anderson-Darling and D'Agostino omnibus tests. Skewness between 0.0 and 0.5 was considered as a minimum (fairly symmetric). The Pearson linear correlation coefficient (*r*) was computed and applied for analysis. Differences between individual flow cytometric histograms were assessed using the Smirnov-Kolmogorov test incorporated in the CELLQuest (Becton Dickinson) software. Statistical analyses were performed using SPSS/11.5 (SPSS, Inc., Chicago, Illinois).



**Figure 4.** Platelet inhibition over the course of time for multiple time point assessments (>2) after loading with 300 mg and maintenance dose of 75 mg of clopidogrel.

## RESULTS

Platelet function before and after clopidogrel therapy was analyzed in all 544 individuals by conventional aggregometry. In most patients (88%), the expression of platelet receptors using flow cytometry also was measured. Using light-transmittance aggregometry and analyzing the change in maximal platelet aggregation with 5  $\mu$ mol of ADP as the agonist, we discovered that the mean change in aggregation from baseline after the initiation of clopidogrel therapy was 41.9%, with a SD of 20.8% (Fig. 1). The histogram of the study population is consistent with a normal, bell-shaped distribution. A negative skewness of  $-0.1$  confirmed almost-ideal symmetric normal distribution, with a very slight trend towards hyporesponsiveness. There were 23 subjects (4.2%) with a change in ADP-induced platelet aggregation greater than two standard deviations above the mean ( $>83.5\%$ ); they were considered to be hyper-responders. Similarly, 26 subjects (4.8%) experienced almost no measurable change in aggregation ( $<2$  standard deviation reductions in aggregation from the mean); they were considered to be hyporesponders. The change in ADP-induced platelet aggregation after the administration of clopidogrel ranged from  $-32\%$  (i.e., greater aggregation than before the administration of clopidogrel) to 94% (almost complete inhibition of aggregation).

When clopidogrel responsiveness was described by the maximal platelet aggregation induced by 5  $\mu$ mol of ADP after clopidogrel (Fig. 2) rather than the change in aggregation, a normal distribution again was observed, with a skewness of 0.35. The mean residual aggregation after the administration of clopidogrel was 37.9%, with a standard deviation of 16.8%. The range of residual ADP-induced aggregation after clopidogrel was 3% to 84%. Platelet aggregation after the administration of clopidogrel was two standard deviations less than the mean in 19 subjects (3.5%) and two standard deviations greater than the mean in 27 subjects (5.0%).

Measures of inhibition of platelet aggregation by light-

**Table 1.** Baseline Characteristics of Standard Responders, Hyper-Responders (>2 SD), and Hyporesponders (<2 SD)

Characteristics	Hyporesponders (n = 18)	Hyper- Responders (n = 18)	Standard Responders (n = 404)	p Value (ANOVA)
Demographics				
Age, yrs (± SD)	62.7 ± 11.1	60.8 ± 11.9	64.0 ± 10.7	0.36
Male gender, n (%)	12 (67)	10 (56)	287 (71)	0.28
Caucasian, n (%)	11 (61)	12 (67)	264 (65)	0.89
Risk factors, n (%)				
Tobacco use	9 (50)	10 (56)	214 (53)	0.77
Hypertension	15 (83)	13 (72)	275 (68)	0.08
Diabetes	7 (39)	7 (39)	177 (44)	0.61
Hypercholesterolemia	11 (61)	10 (54)	233 (58)	0.8
Family history	12 (67)	11 (61)	281 (69)	0.67
Medical history, n (%)				
Previous MI	4 (22)	4 (22)	96 (24)	0.74
Previous stroke	2 (11)	1 (6)	30 (7)	0.5
Heart failure	5 (27)	4 (22)	33 (8)	0.36
Heart surgery	2 (11)	2 (11)	36 (9)	0.75
Medications, n (%)				
Beta-blockers	6 (33)	8 (44)	140 (35)	0.45
ACE inhibitors	4 (22)	4 (22)	137 (35)	0.28
Calcium-channel blockers	3 (17)	5 (28)	87 (20)	0.22
AT-receptor antagonists	3 (17)	4 (22)	86 (20)	0.6
Diuretics	4 (22)	3 (17)	71 (18)	0.42
Statins	9 (50)	10 (54)	221 (55)	0.51
Atorvastatin	5/9 (56)	6/10 (60)	134/221 (61)	0.47
Antidepressants	3 (17)	2 (11)	45 (11)	0.2
Aggregometry (5μM ADP)				
Platelet aggregation (%)	67 ± 13	68 ± 10	65 ± 10	0.6

Data are presented as the mean value ± SD or percentage of patients.

ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; ANOVA = analysis of variance; AT = angiotensin; MI = myocardial infarction.

transmittance aggregometry and platelet activation by platelet/endothelial cell adhesion molecule-1 expression determined by flow cytometry were available from 374 subjects at identical time points from the same blood samples (Fig. 3). Regression analysis revealed a moderate positive correlation ( $r = 0.51$ ,  $p = 0.023$ ) between these measures of platelet aggregation and activation-dependent receptor expression after the administration of clopidogrel.

Of the 544 subjects studied, 380 had more than one measurement of platelet function after the maximal antiplatelet effects of clopidogrel were achieved (Fig. 4). Most of these serial measurements were within 48 h of the initiation of therapy with a loading dose. Only a few patients ( $n = 30$ ) were evaluated after 30 days of receiving daily clopidogrel. No significant change in the mean level of inhibition of ADP-induced platelet aggregation was observed over the course of time, although the small numbers studied at the longest durations of therapy limit the ability to make any definitive conclusions.

Hyporesponders and hyper-responders to clopidogrel, as determined by change in ADP-induced platelet aggregation, did not differ significantly in clinical characteristics from those whose responses were in the standard range (Table 1). Hyporesponders to clopidogrel had a trend toward a greater prevalence of hypertension. Platelet activity before the administration of clopidogrel, which was defined

by baseline platelet aggregation response to ADP, did not appear to be associated with the response to clopidogrel (Table 1).

In some of the subjects included in this analysis, up to six separate measures of platelet inhibition were conducted. Whether subjects who were hyporesponders or hyper-responders to ADP-induced aggregation also were hyporesponsive or hyper-responsive to other tests of platelet inhibition was analyzed (Table 2). Of the 26 patients identified as hyporesponders, 50% to 89% met the criteria for being hyporesponsive when other measures of platelet inhibition were used. Similarly, of the 23 patients identified as hyper-responsive by their aggregation response, 51% to 74% also remained hyper-responsive when additional tests of platelet function were used.

## DISCUSSION

This study, which comprises the largest population base of its kind to date, demonstrates a marked variability in response after standard dosing of the antiplatelet agent clopidogrel. The normal distribution of response to clopidogrel is consistent with the large number of recognized and unrecognized genetic and environmental factors that influence platelet function and responsiveness to other antiplatelet therapies. The clinical implications of these *ex vivo*

**Table 2.** Number of Patients Who Were Hyporesponsive or Hyper-Responsive to Clopidogrel Based on the Change in ADP-Induced Aggregation Who Were Determined to be Hyporesponsive and Hyper-Responsive by Other Methods of Measuring Platelet Inhibition

Group*	n	GP IIb/IIIa	P-Selectin	PECAM-1	VTR	CD151-CD14
Hyporesponders	26/544	15 (58%)	18 (69%)	23 (89%)	15 (58%)	13 (50%)
Hyper-responders	23/544	13 (57%)	15 (65%)	16 (70%)	17 (74%)	12 (51%)

\*Based on (2SD) ADP-induced aggregation hyporesponders, hyper-responders definition, and after quality control and quality assurance sample validation. CD151-CD14 = formation of platelet-monocyte aggregates; GP = glycoprotein; PECAM-1 = platelet/endothelial cell adhesion molecule-1; VTR = vitronectin receptor.

findings are unknown but likely are to be important, based on the high prevalence of atherosclerotic disease and the central role of antiplatelet therapies in the prevention and treatment of its complications.

Clopidogrel, administered with or without aspirin, has been evaluated in prospective, placebo-controlled trials involving more than 30,000 patients to date (11-13). Treatment with the combination of clopidogrel and aspirin for as short a period as one year can decrease the occurrence of death, myocardial infarction, and stroke by 20% to 27% compared with the use of aspirin alone (12,13). However, despite the recognition for several decades of wide interpatient variability in the measured response to antiplatelet therapy, a true relationship between any test of platelet inhibition and clinical outcomes has yet to be proven.

Clopidogrel "non-responsiveness" has been reported to be present in as little as 5% to as many as 56% of patients who are undergoing coronary stenting. Previous studies (4-6) labeled patients as non-responders based on the arbitrary definitions of the change in ADP-induced platelet aggregation before and after the start of clopidogrel therapy. In this study, we chose to identify responsiveness to clopidogrel in a manner more consistent with standard laboratory practice when describing normally distributed values, with abnormal values being those greater and less than two standard deviations from the mean. By doing so, we found 4.8% of subjects to be hyporesponsive and 4.3% to be hyper-responsive to clopidogrel.

The definition of clopidogrel response in our analyses is also arbitrary but seems more physiologic for assessment in the large cohorts compared with the single-patient measures based only on the differences in the platelet activity. On the basis of the present data, the concept of triaging patients into "responder" and "non-responder" must be performed with great caution. The present dataset reveals a normal, bell-shaped distribution of clopidogrel response, thereby suggesting too wide of a range of response to be simply dichotomized. We were not able to identify any clinical characteristics associated with hyper-responsiveness or hyporesponsiveness, nor were we able to confirm the results of previous investigators who reported a relationship between baseline platelet activity and response to clopidogrel (6). Although, like other investigators, we focused on the use of standard light-transmittance aggregometry in PRP as a means of evaluating individual responsiveness to clopidogrel, we also used a wide selection of other studies of platelet function to assess a patient's responsiveness to clopidogrel. We found a relatively strong correlation be-

tween the measured inhibition of platelet aggregation and the inhibition of platelet activation using flow cytometry but also showed that the classification of individuals as hyporesponders or hyper-responders does vary depending on the test used. All of these measures of platelet function are limited in their applicability to clinical practice because they require specialized equipment, complicated sample preparation, and technical expertise. Although several point-of-care tests are available, their clinical value has yet to be proven. The term "clopidogrel resistance" (as opposed to clopidogrel response variability) can only be accurately used when and if there is documentation that administration of clopidogrel not only results in a lack of platelet inhibition but also yields less clinical benefit than in patients achieving greater levels of platelet inhibition.

**Study limitations.** Several limitations merit mention. First, we present post-hoc second analyses; therefore, the data were not collected in the prospective fashion. Second, different protocols were used for the primary studies. High frequency of the use of concomitant medications may have affected the platelet characteristics. Despite the fact that in most patients platelets were assessed with more than 10 characteristics, some established biomarkers of platelet activity, such as beta-thromboglobulin, platelet factor-4, thromboxane, and nitric oxide, were not measured. Importantly, different doses of aspirin (if any) were used, although this should not influence ADP-induced effects. Finally, clinical outcome data were available for the present analyses.

**Conclusions.** The results of this study demonstrate that in patients treated with clopidogrel, there is a very large range of responsiveness to ex vivo testing that represents a normally distributed bell-shaped curve. If these ex vivo results correspond to clinical outcomes, which remains to be proven, it is likely that a small but significant portion of patients are receiving inadequate protection from thrombotic events despite currently standard antiplatelet therapy, whereas a similar proportion may be at higher risk for bleeding complications. There is a great need for clinical trials to prospectively identify a measure of platelet function that can consistently and reproducibly measure the response of a patient to an antiplatelet therapy and then be able to correlate that result to the risk of adverse clinical outcomes. Once this is established, individualized treatment regimens should then be studied in an attempt to maximize the benefit and minimize the risk to the tens of millions of patients treated with daily, life-long antiplatelet therapy.

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