■ ORIGINAL CONTRIBUTION

High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients With Acute Coronary Syndromes Undergoing PCI

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S EVERAL STUDIES HAVE SHOWN that high residual platelet reactivity during clopidogrel treatment is predictive of major cardiovascular events in patients undergoing percutaneous coronary intervention (PCI).[1-14] However, there is no standardized technique among ex vivo platelet function tests, and in studies using the same platelet function test, cutoff values for high on-treatment platelet reactivity established by receiver operating characteristic curve analysis are variable. Consequently, the hypothesis that the risk of thrombotic events increases markedly above a critical cut point of platelet reactivity on in vitro tests is not yet proven. Moreover, most studies have included heterogeneous populations with short follow-up, and few data exist for patients with acute coronary syndromes (ACS) undergoing an invasive procedure.

For editorial comment see p 1260.

Context High residual platelet reactivity (HRPR) in patients receiving clopidogrel has been associated with high risk of ischemic events after percutaneous coronary intervention (PCI).

Objective To test the hypothesis that HRPR after clopidogrel loading is an independent prognostic marker of risk of long-term thrombotic events in patients with acute coronary syndromes (ACS) undergoing an invasive procedure and antithrombotic treatment adjusted according to the results of platelet function tests.

Design, Setting, and Patients Prospective, observational, referral center cohort study of 1789 consecutive patients with ACS undergoing PCI from April 2005 to April 2009 at the Division of Cardiology of Careggi Hospital, Florence, Italy, in whom platelet reactivity was prospectively assessed by light transmittance aggregometry.

Interventions All patients received 325 mg of aspirin and a loading dose of 600 mg of clopidogrel followed by a maintenance dosage of 325 mg/d of aspirin and 75 mg/d of clopidogrel for at least 6 months. Patients with HRPR as assessed by adenosine diphosphate test ($\geq$70% platelet aggregation) received an increased dose of clopidogrel (150-300 mg/d) or switched to ticlopidine (500-1000 mg/d) under adenosine diphosphate test guidance.

Main Outcome Measures The primary end point was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up. Secondary end points were stent thrombosis and each component of the primary end point.

Results The primary end point event rate was 14.6% (36/247) in patients with HRPR and 8.7% (132/1525) in patients with low residual platelet reactivity (absolute risk increase, 5.9%; 95% CI, 1.6%-11.1%; P=.003). Stent thrombosis was higher in the HRPR group compared with the low residual platelet reactivity group (6.1% [15/247] vs 2.9% [44/1525]; absolute risk increase, 3.2%; 95% CI, 0.4%-6.7%; P=.01). By multivariable analysis, HRPR was independently associated with the primary end point (hazard ratio, 1.49; 95% CI, 1.08-2.05; P=.02) and with cardiac mortality (hazard ratio, 1.81; 95% CI, 1.18-2.76; P=.006).

Conclusion Among patients receiving platelet reactivity–guided antithrombotic medication after PCI, HRPR status was significantly associated with increased risk of ischemic events at short- and long-term follow-up.

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The Responsiveness to Clopidogrel and Stent Thrombosis 2–ACS (RECLOSE 2–ACS) study tested the hypothesis that high residual platelet re-

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activity after clopidogrel loading is an independent prognostic marker of risk of long-term thrombotic events in patients with ACS undergoing an invasive procedure and receiving long-term antithrombotic treatment adjusted according to the results of platelet function tests.

METHODS

Study Design

We performed a prospective, observational, single-center cohort study of consecutive patients with ACS undergoing an invasive procedure in whom platelet reactivity after clopidogrel loading was prospectively assessed.

Patient Population

Consecutive patients undergoing coronary stent implantation for ACS from April 2005 to April 2009 at the Division of Cardiology of Careggi Hospital, Florence, Italy, were enrolled in this study. Acute coronary syndromes included unstable angina with ST-segment changes, non–ST-segment elevation acute myocardial infarction, and ST-segment elevation acute myocardial infarction (STEMI). All patients were considered eligible for the study irrespective of clinical presentation of ACS or coronary anatomy.

Thus, patients with multivessel disease requiring multivessel intervention in the same procedure or in a staged procedure were included. The only exclusion criteria were in-hospital death that was not due to stent thrombosis and anticipated nonadherence to dual antiplatelet treatment for at least 6 months.

The study was approved by the local ethics committee. All patients gave written informed consent.

Platelet Reactivity Assessment

Platelet reactivity assessment was made by light transmittance aggregometry (APACT4, Helena Laboratories, Milan, Italy) using adenosine diphosphate (ADP) as an agonist. Blood samples anticoagulated with 0.109M sodium citrate (ratio, 9:1) were obtained 12 to 18 hours after a 600-mg clopidogrel loading dose. For patients receiving both the loading dose of clopidogrel and a glycoprotein IIb/IIIa inhibitor in the catheterization laboratory, blood samples were obtained after 6 days, while patients were receiving a 75-mg/d maintenance dosage of clopidogrel and 325 mg/d of aspirin. Platelet-rich plasma, obtained by centrifuging whole blood for 10 minutes at 200g, was stimulated with 10μM ADP. The 100% line was set using platelet-poor plasma and the 0 baseline established with platelet-rich plasma (adjusted from 180×10^9/L to 300×10^9/L). Platelet aggregation (according to the Born method) was evaluated considering the maximal percentage of platelet aggregation in response to stimulus. The coefficient of variation of ADP platelet aggregation was 6.8%.[6,8,9] High residual platelet reactivity by ADP test was defined as platelet aggregation of 70% or greater.[6]

PCI and Antiplatelet Management

All interventions were performed according to current standards, and the type of stent implanted and the use of glycoprotein IIb/IIIa inhibitors were at the discretion of the operator. All patients received 325 mg of aspirin and a loading dose of 600 mg of clopidogrel followed by a maintenance dosage of 325 mg/d of aspirin and 75 mg/d of clopidogrel for at least 6 months. Patients taking a maintenance regimen of ticlopidine or clopidogrel at the time of admission received a reloading dose of 600 mg of clopidogrel. Patients with high residual platelet reactivity by ADP test received an increased long-term dosage of clopidogrel (150-300 mg/d) or switched to ticlopidine (500-1000 mg/d) under ADP test guidance, with the goal of reaching an ADP test result of less than 70% platelet aggregation.

End Points

The primary end point of the study was a composite of ischemic events including cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up. Patients with more than 1 event were assigned the highest-ranked event according to the previous list. Key secondary end points were stent thrombosis, defined according to the Academic Research Consortium criteria,[15] and the individual components of the primary end point.

All deaths were considered cardiac unless an unequivocal noncardiac cause could be documented. Myocardial infarction definition included the following criteria: electrocardiographic changes consistent with myocardial infarction or cardiac biomarker elevation (creatine kinase–MB or troponin I 3 times higher than the upper normal limit on 2 measurements) or cardiac biomarker reelevation in patients with pre-PCI values higher than the upper normal limits (at least 50% higher than the previous nadir, with documentation that cardiac biomarkers were decreasing before PCI). Urgent coronary revascularization included intervention due to recurrence of ACS. Stroke was defined as an acute neurological deficit lasting more than 24 hours.

All events were adjudicated by an event adjudication committee whose members (R.M., P.B., and R.A.) were blinded for platelet function data.

Follow-up

All patients had scheduled examinations at 1, 6, and 12 months and then annually thereafter. Adherence to antiplatelet treatment was assessed during scheduled or unscheduled examinations. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries were entered into the prospective database.

Statistical Analysis

Based on the results of the RECLOSE 1 study,[6] the current study was powered to demonstrate an increase in the primary end point from an expected 10% in patients with low residual platelet reactivity by ADP test to 20% in patients with high residual platelet reactivity. With this assumption, the statistical power was greater than 90% based on a maximum sample size of

1298 patients for the primary end point and 1596 for cardiac mortality.

Discrete data are summarized as frequencies and continuous data are expressed as means and standard deviations or medians and interquartile ranges (IQRs) as appropriate. The χ^2 test was used for comparison of categorical variables, and the unpaired, 2-tailed *t* test or Mann-Whitney rank sum test was used to test differences among continuous variables. To control for type I error in multiple comparisons, the Bonferroni-adjusted significance level was used for the 5 secondary end point outcomes. Survival curves were generated with the Kaplan-Meier method, and the difference between groups was assessed by log-rank test. A landmark analysis was computed by the Kaplan-Meier method for the primary end point and for cardiac mortality using a starting point of 6 months after the index procedure. We selected the 6-month point as a landmark according to the prespecified exclusion criterion of anticipated nonadherence to dual antiplatelet treatment for at least 6 months.

The outcomes of 6-month event-free (primary end point or cardiac death) patients were evaluated at longer-term follow-up in the 2 study groups. The multivariable analyses to evaluate the independent contribution of clinical, angiographic, procedural, and platelet reactivity variables to the primary end point and cardiac mortality were performed by the forward stepwise Cox proportional hazards model. High platelet reactivity according to the chosen criterion (ADP test result ≥70%) was entered as a dichotomous variable. The other variables entered into the model were as follows: age, male sex, body mass index of 30 or higher, smoking, diabetes mellitus, hypertension, hypercholesterolemia, history of myocardial infarction, serum creatinine level higher than 1.50 mg/dL (to convert values to μmol/L, multiply by 88.4), left ventricular ejection fraction of less than 40%, Killip class of III or IV on admission, 3-vessel coronary disease, use of

drug-eluting stents, total stent length, multivessel PCI, and use of abciximab. The proportional hazard assumption was assessed and satisfied graphically by plotting log (–log) survival curves against log survival time for each predictor category and verifying whether curves were parallel, and in addition, using time-dependent covariates. Cox regression analysis was performed to assess time-dependent covariates. No significant time-dependent predictor was found. Multicollinearity was assessed using collinearity diagnostics. The variance inflation factors showed no significant collinearity among the covariates (<2.0). The Cox proportional hazards model was used to test interaction among covariates. A propensity score analysis was performed with a logistic regression model from which the probability for high residual platelet reactivity to the ADP test was calculated for each patient. The variables that were significantly different between the 2 groups and those that are known to affect platelet reactivity were incorporated in the model: age, male sex, body mass index of 30 or higher, smoking, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary artery disease, history of myocardial infarction, serum creatinine level higher than 1.50 mg/dL, left ventricular ejection fraction less than 40%, Killip class of III or IV on admission, 3-vessel coronary disease, previous PCI, previous coronary surgery, and STEMI. Model discrimination was assessed with the C statistic and goodness of fit with the Hosmer-Lemeshow test. Thereafter, a Cox multivariate analysis was performed to adjust high residual platelet reactivity for propensity score used as a continuous covariate.

A propensity score–matched analysis (3:1) was also performed because of the expected differences in baseline characteristics between patients with high and low residual platelet reactivity. An optimal data matching technique without replacement was performed with a random order using the radius-matching

algorithm for propensity score difference with a caliper of 0.5. Bias reduction was assessed by comparing the standardized difference for propensity score and the other covariates before and after matching between the 2 groups (a value <10% after matching indicates inconsequential imbalance). After matching, the standardized difference for propensity score changed from 53.3% to 4.8% and for the other covariates to less than 10%. Two-year outcomes for the primary end point, cardiac mortality, and stent thrombosis were assessed after matching by χ^2 test. The risk of overfitting was controlled by using a ratio of at least 1:10 for the number of explanatory variables and sample size. In addition, in the second Cox multivariable model, the adjustment of high residual platelet reactivity for propensity score (using 2 covariates) minimized the overfitting risk. *P*<.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with SPSS software, version 19 (IBM Corp, Somers, NY).

RESULTS

From April 2005 to April 2009, 1931 consecutive patients admitted for ACS underwent PCI at Careggi Hospital (**FIGURE 1**). Among these patients, 1789 were enrolled in the study, while 142 were excluded for the following reasons: anticipated nonadherence to dual antiplatelet treatment (93 patients), unavailability of platelet function tests because of in-hospital death due to cardiogenic shock or congestive heart failure, or thrombocytopenia (48 patients), and refusal to participate (1 patient). Baseline patient characteristics are presented in **TABLE 1**. The incidence of high residual platelet reactivity by ADP test after clopidogrel loading was 14%. Patients with high residual platelet reactivity were older than patients with low residual platelet reactivity and had a higher incidence of diabetes mellitus, hypercholesterolemia, and history of previous myocardial infarction, while STEMI was more fre-

Figure 1. Study Flow
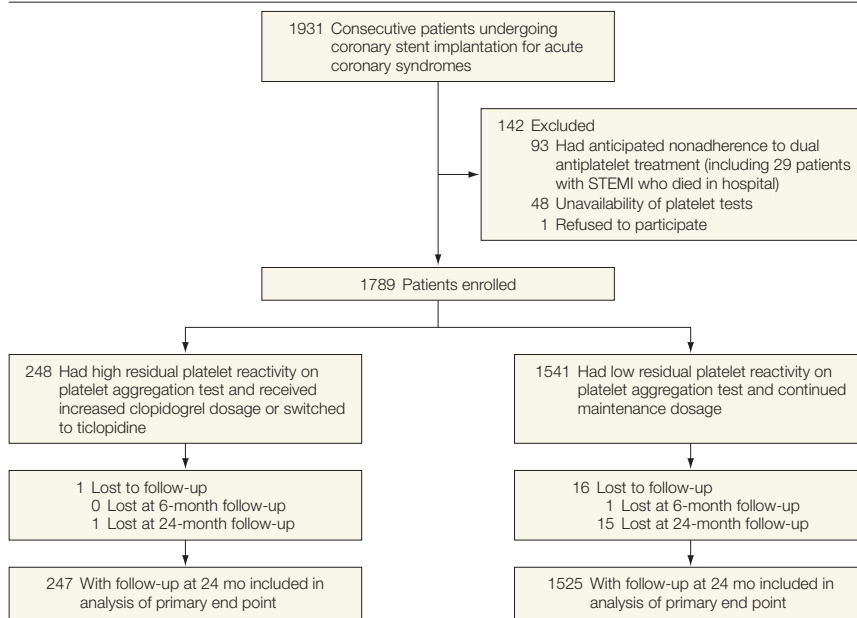
STEMI indicates ST-elevation myocardial infarction.

Table 1. Baseline Characteristics

Characteristics	No. (%) of Participants[a]			
	Total (N = 1789)	LRPR (n = 1541)	HRPR (n = 248)	P Value[b]
Age, mean (SD), y	69.0 (11.8)	68.6 (11.8)	71.7 (11.3)	<.001
Aged ≥75 y	664 (37)	537 (35)	127 (51)	<.001
Male	1423 (80)	1232 (80)	191 (77)	.29
Body mass index, mean (SD)[c]	26.3 (3.8)	26.3 (3.8)	26.6 (3.9)	.25
Body mass index ≥30[c]	295 (16)	249 (16)	46 (18)	.35
Smokers	437 (24)	389 (25)	48 (19)	.045
Hypertension	1021 (57)	870 (56)	151 (61)	.19
Diabetes mellitus	355 (20)	285 (19)	70 (28)	<.001
Hypercholesterolemia	801 (45)	667 (43)	134 (54)	.002
Previous myocardial infarction	324 (18)	254 (16)	70 (28)	<.001
Previous PCI	273 (15)	226 (15)	47 (19)	.08
Previous coronary surgery	91 (5)	75 (5)	16 (6)	.29
ST-elevation acute myocardial infarction	829 (46)	747 (48)	82 (33)	<.001
Creatinine >1.50 mg/dL	188 (10)	160 (10)	28 (11)	.67
LVEF, mean (SD), %	45.3 (11.3)	45.6 (11.1)	43.1 (12.3)	.001
LVEF ≤40%	552 (31)	455 (29)	97 (39)	.002
Killip class III-IV	104 (6)	89 (6)	15 (6)	.87
ADP test result, median (range), %	46 (27-61)	41 (24-54)	76 (72-81)	<.001[d]
Aspirin at discharge	1747 (98)	1508 (98)	239 (96)	.15
Clopidogrel at discharge	1789 (100)	1541 (100)	248 (100)	>.99
Warfarin at discharge	36 (2)	31 (2)	5 (2)	>.99
Statin at discharge	1628 (91)	1408 (91)	220 (89)	.17
Proton pump inhibitor at discharge	1181 (66)	1012 (66)	169 (68)	.46

Abbreviations: ADP, adenosine diphosphate; HRPR, high residual platelet reactivity; LRPR, low residual platelet reactivity; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
[a]Data are expressed as No. (%) of participants unless otherwise indicated.
[b]The χ^2 test was used for comparison of categorical variables and the unpaired 2-tailed t test for continuous variables unless otherwise indicated.
[c]Calculated as weight in kilograms divided by height in meters squared.
[d]Comparison between groups was performed by the Mann-Whitney rank sum test.

quent in the low residual platelet reactivity group. Moreover, congestive heart failure and a left ventricular ejection fraction of less than 40% were more frequent in the high residual platelet reactivity group.

The median value of ADP test results after clopidogrel loading was 41% (IQR, 24%-54%) in the low residual platelet reactivity group and 76% (IQR, 72%-81%) in the high residual platelet reactivity group. Among patients with high residual platelet reactivity after clopidogrel loading, the median value of the ADP test result decreased to 64% (IQR, 54%-75%; $P<.001$) after treatment adjustment, but 94 patients (38%) still had an ADP test result of 70% or greater. **TABLE 2** summarizes the angiographic and procedural characteristics.

Follow-up

The 2-year follow-up rate was 99% (median follow-up length, 2.8 years [IQR, 2.3-3.7 years]). The follow-up rates were 99.6% and 98.9% ($P=.31$) in patients with and without high residual platelet reactivity, respectively. At 6 months, adherence to dual antiplatelet treatment was very high: 97% of patients were taking aspirin and a thienopyridine (97% of the low residual platelet reactivity group and 99% of the high residual platelet reactivity group). At a median follow-up of 2.8 years, 952 patients (63%) in the low residual platelet reactivity group and 168 patients (68%) in the high residual platelet reactivity group were taking 2 antiplatelet agents. Most patients in both groups took statins, β-blockers, and angiotensin-converting enzyme inhibitors that were prescribed according to the recommendations of current guidelines.

Clinical Outcome

TABLE 3 summarizes the 2-year clinical outcome. The primary end point event rate was 14.6% (36/247) in the high residual platelet reactivity group and 8.7% (132/1525) in the low residual platelet reactivity group (absolute risk increase, 5.9%; 95% CI, 1.6%-11.1%; $P=.003$). Negative and positive

predictive values were 91% (95% CI, 90%-93%) and 15% (95% CI, 11%-20%), respectively. The difference in the primary end point event rate was driven by the difference in cardiac mortality, which was 9.7% in the high residual platelet reactivity group and 4.3% in the low residual platelet reactivity group (absolute risk increase, 5.5%; 95% CI, 1.9%-9.7%; $P<.001$); there were no differences in the other components of the primary end point. Among patients with high residual platelet reactivity after clopidogrel loading, there were no differences either in the primary end point rate or in cardiac mortality among patients with an ADP test result of less than 70% after treatment adjustment vs patients with a persistent ADP test result of 70% or greater (primary end point event rates, 14.4% and 14.9%, respectively; $P=.91$; cardiac mortality rates, 8.5% and 11.7%, respectively; $P=.41$). **FIGURE 2** shows the long-term estimated risk of the primary end point and cardiac mortality. The estimated risk of a primary end point event was 27.5% (95% CI, 18.3%-36.7%) in the high residual platelet reactivity group and 14.5% (95% CI, 12.1%-16.9%) in the low residual platelet reactivity group ($P<.001$). The estimated risk of cardiac mortality was 12.7% (95% CI, 8.3%-17.1%) in the high residual platelet reactivity group and 6.9% (95% CI, 5.4%-8.4%) in the low residual platelet reactivity group ($P<.001$). The landmark analysis using the prespecified starting point of 6 months showed that the differences between groups in the primary end point and in cardiac mortality emerged both in the short-term follow-up as well as from 6 months to long term (**FIGURE 3**).

In the entire study population, the stent thrombosis rate was 3.3% (59/1772) (Table 3). The stent thrombosis rate was 2-fold higher in the high residual platelet reactivity group (6.1% [15/247] vs 2.9% [44/1525]; absolute risk increase, 3.2%; 95% CI, 0.4%-6.7%; $P=.01$).

By multivariable analysis, high residual platelet reactivity was independently associated with the primary end point (hazard ratio [HR], 1.49; 95% CI, 1.08-2.05; $P=.02$) and with cardiac mortality (HR, 1.81; 95% CI, 1.18-2.76; $P=.006$) (**TABLE 4**) and remained significantly associated with the primary end point and cardiac mortality after propensity score adjustment (*C* statistic, 0.65; 95% CI, 0.62-0.69; $P=.81$ for Hosmer-Lemeshow test): the HR for primary end point events was 1.47 (95% CI, 1.06-2.04; $P=.02$) and the HR for cardiac mortality was 1.63 (95% CI, 1.06-2.51; $P=.03$). No significant interaction was found between high residual platelet reactivity and the other covariates. In the propensity score–matched analysis that included 992 patients (100% of the high residual plate-

Table 2. Angiographic and Index Procedure Characteristics

	No. (%) of Participants[a]			
Characteristics	Total (N = 1789)	LRPR (n = 1541)	HRPR (n = 248)	P Value[b]
Multivessel coronary disease	1020 (57)	858 (56)	162 (65)	.004
3-Vessel disease	487 (27)	405 (26)	82 (33)	.03
Thrombus-containing lesions	561 (31)	495 (32)	66 (27)	.08
Multivessel PCI	551 (31)	455 (29)	96 (39)	.004
2-Vessel PCI	411 (23)	343 (22)	68 (27)	
3-Vessel PCI	128 (87)	103 (7)	25 (10)	
Treated vessel				
Left anterior descending artery	938 (52)	793 (51)	145 (58)	.04
Right coronary artery	710 (40)	614 (40)	96 (39)	.74
Circumflex coronary artery	597 (33)	503 (33)	94 (38)	.10
Left main	125 (7)	103 (7)	22 (9)	.20
Ramus	57 (3)	48 (3)	9 (4)	.67
Thrombectomy	417 (23)	370 (24)	47 (19)	.08
No. of stents per patient, mean (SD)	1.8 (1.1)	1.8 (1.1)	1.9 (1.1)	.09
Total stent length, mean (SD), mm	32.9 (26.0)	32.4 (25.9)	36.0 (26.5)	.04
Treatment with drug-eluting stent	917 (51)	784 (51)	133 (54)	.42
Abciximab use	1227 (69)	1064 (69)	163 (66)	.30
Hospital length of stay, mean (SD), d	3.6 (3.1)	3.5 (3.0)	4.1 (3.7)	.005

Abbreviations: HRPR, high residual platelet reactivity; LRPR, low residual platelet reactivity; PCI, percutaneous coronary intervention.
[a]Data are expressed as No. (%) of participants unless otherwise indicated.
[b]The χ^2 test was used for comparison of categorical variables and the unpaired 2-tailed *t* test for continuous variables.

Table 3. Two-Year Clinical Outcomes

	No. (%) of Participants			
Outcomes	Total (n = 1772)	LRPR (n = 1525)	HRPR (n = 247)	P Value[a]
Primary end point	168 (9.5)	132 (8.7)	36 (14.6)	.003
Cardiac death	89 (5)	65 (4.3)	24 (9.7)	<.001
Myocardial infarction	41 (2.3)	33 (2.2)	8 (3.2)	.30
Urgent coronary revascularization	16 (0.9)	15 (1.0)	1 (0.4)	.71[b]
Stroke	22 (1.2)	19 (1.2)	3 (1.2)	>.99[b]
Stent thrombosis	59 (3.3)	44 (2.9)	15 (6.1)	.01
Definite	30 (1.7)	23 (1.5)	7 (2.8)	.13
Probable	15 (0.8)	11 (0.7)	4 (1.6)	.15
Possible	14 (0.9)	10 (0.7)	4 (1.6)	.11

Abbreviations: HRPR, high residual platelet reactivity; LRPR, low residual platelet reactivity.
[a]The χ^2 test was used for comparison unless otherwise indicated.
[b]By Fisher exact test.

let reactivity group and 48% of the low residual platelet reactivity group were successfully matched) (TABLE 5), the 2-year primary end point event rate and cardiac mortality rate were significantly higher in the high residual platelet reactivity group compared with the low residual platelet reactivity group (primary end point event rate, 14.6% [36/246] vs 9.2% [68/737]; *P* = .02 and cardiac mortality rate, 9.7% [24/246] vs 5.3% [39/737]; *P* = .01). Again, in the

matched cohort, the stent thrombosis rate was higher in patients with high residual platelet reactivity compared with patients with low residual platelet reactivity (6.1% [15/246] vs 3.1% [23/737], respectively; *P* = .04).

COMMENT

The main findings of this study can be summarized as follows: (1) The incidence of high residual platelet reactivity using ADP as an agonist after a

600-mg clopidogrel loading dose in patients with ACS undergoing an invasive procedure is relatively low (14%); (2) residual platelet reactivity remains high in 38% of patients after treatment adjustment with first-generation thienopyridines; (3) normalization of the ADP test result after treatment adjustment is not associated with a better outcome vs a persistent abnormal ADP test result; and (4) high residual platelet reactivity after

Figure 2. Kaplan-Meier Survival Curves for Primary End Point Events and for Cardiac Mortality in Patients With HRPR and LRPR
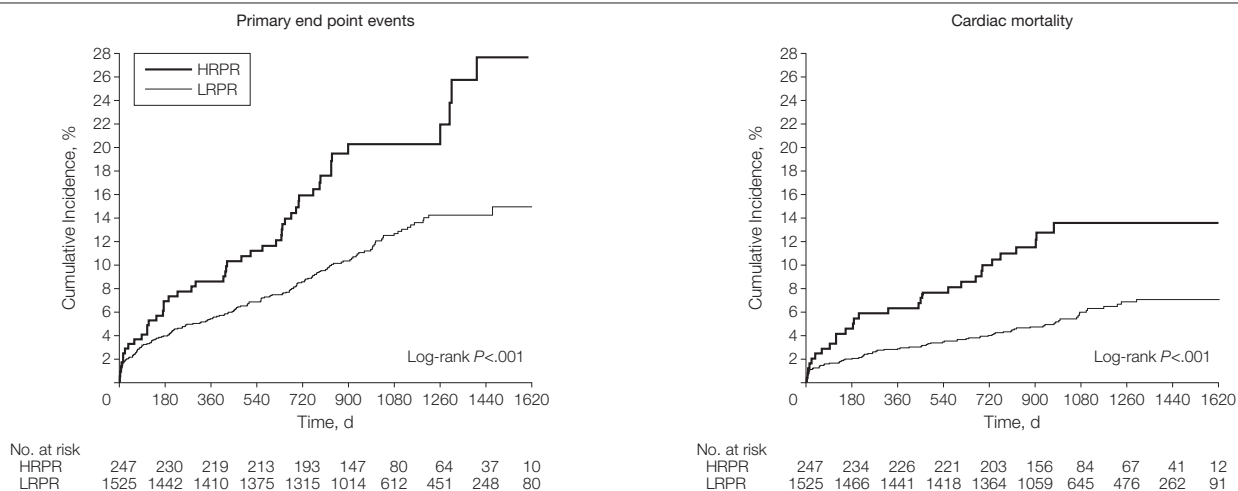
HRPR indicates high residual platelet reactivity; LRPR, low residual platelet reactivity. Primary end point events included cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke.

Figure 3. Kaplan-Meier Landmark Analysis Survival Curves for Primary End Point Events and for Cardiac Mortality Beginning at 6 Months in Patients With HRPR and LRPR
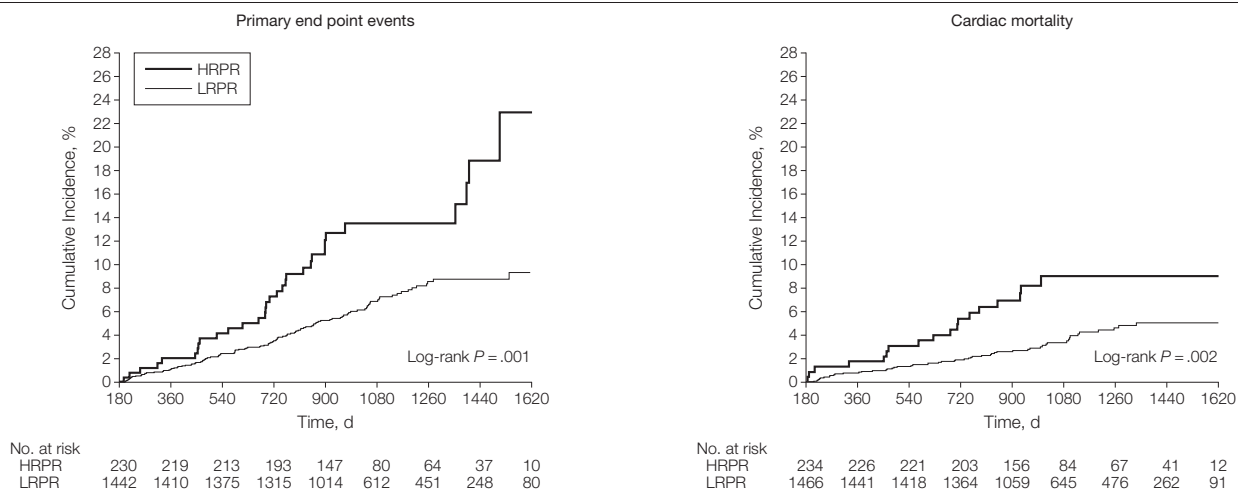
HRPR indicates high residual platelet reactivity; LRPR, low residual platelet reactivity. Primary end point events included cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke.

clopidogrel loading is associated with increased risk of short- and long-term ischemic events, including stent thrombosis.

The incidence of 14% of high residual platelet reactivity as revealed in this study is consistent with previous studies using light transmittance aggregometry, 10μM of ADP as an agonist, and a cutoff value of 70%.[6,8,9] Unlike previous studies that included patients with stable coronary artery disease, this study included only patients with ACS, who may have higher baseline platelet reactivity vs stable patients. The finding of similar incidence of high residual platelet reactivity in this study suggests that the potential difference in baseline platelet reactivity between patients with stable coronary artery disease and those with ACS

Table 4. Univariable and Multivariable-Adjusted Predictors of Long-term Primary End Point Events and Cardiac Death

Variables	No. of Events/ No. of Participants[a]	Unadjusted Hazard Ratio (95% CI)	P Value[b]	Multivariable-Adjusted Hazard Ratio (95% CI)	P Value[b]
		Primary End Point			
HRPR	49/247	1.82 (1.33-2.50)	<.001	1.49 (1.08-2.05)	.02
Age, mean (SD), per y	74 (11)	1.05 (1.04-1.06)	<.001	1.04 (1.03-1.05)	<.001
Male sex	169/1411	0.76 (0.56-1.03)	.08		
Body mass index ≥30[c]	31/292	0.92 (0.63-1.34)	.66		
Smokers	45/431	0.75 (0.54-1.04)	.08		
Diabetes mellitus	57/355	1.38 (1.02-1.86)	.04		
Hypertension	129/1015	1.01 (0.78-1.32)	.92		
Hypercholesterolemia	97/792	0.94 (0.72-1.23)	.66		
Family history of coronary disease	11/121	0.66 (0.36-1.22)	.18		
History of myocardial infarction	67/322	2.02 (1.51-2.68)	<.001	1.50 (1.12-2.02)	.007
Creatinine >1.5 mg/dL	38/185	1.77 (1.25-2.50)	.003	1.52 (1.07-2.17)	.02
LVEF <40%	114/548	2.52 (1.94-3.27)	<.001	1.67 (1.25-2.23)	.001
Killip class III-IV on admission	32/103	3.41 (2.34-4.96)	<.001	2.43 (1.62-3.64)	<.001
3-Vessel coronary disease	86/486	1.72 (1.31-2.25)	<.001		
Use of abciximab	162/1218	1.24 (0.93-1.67)	.15		
Use of drug-eluting stents	127/913	1.04 (0.80-1.36)	.76		
Total stent length, mean (SD), mm	38 (30)	1.01 (1.01-1.02)	.004		
Multivessel PCI	90/549	1.50 (1.15-1.96)	.003		
		Cardiac Death			
HRPR	29/247	2.24 (1.47-3.42)	<.001	1.81 (1.18-2.76)	.006
Age, mean (SD), per y	77 (10)	1.08 (1.06-1.10)	<.001	1.06 (1.04-1.08)	<.001
Male sex	85/1411	0.76 (0.49-1.17)	.21		
Body mass index ≥30[c]	10/292	0.54 (0.28-1.04)	.07		
Smokers	20/431	0.65 (0.40-1.05)	.08		
Diabetes mellitus	37/355	1.99 (1.34-2.95)	.001		
Hypertension	75/1015	1.49 (1.01-2.20)	.045		
Hypercholesterolemia	54/792	1.14 (0.79-1.65)	.49		
Family history of coronary disease	6/121	0.74 (0.32-1.67)	.47		
History of myocardial infarction	35/322	2.08 (1.40-3.10)	<.001		
Creatinine >1.5 mg/dL	26/185	2.57 (1.66-3.98)	<.001	1.91 (1.22-2.99)	.005
LVEF <40%	69/548	3.76 (2.57-5.48)	<.001	2.16 (1.43-3.26)	<.001
Killip class III-IV on admission	21/103	4.50 (2.80-7.23)	<.001	2.72 (1.63-4.52)	<.001
3-Vessel coronary disease	55/486	2.59 (1.79-3.75)	<.001	1.74 (1.19-2.54)	.004
Use of abciximab	83/1218	1.30 (0.86-1.98)	.22		
Use of drug-eluting stents	66/913	1.15 (0.79-1.68)	.46		
Total stent length, mean (SD), mm	39 (31)	1.01 (1.01-1.02)	.01		
Multivessel PCI	55/549	2.13 (1.47-3.08)	<.001		

Abbreviations: HRPR, high residual platelet reactivity; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
[a] Continuous variables are presented as mean (SD) in patients who had a primary end point event or cardiac death.
[b] By Cox proportional hazards model.
[c] Calculated as weight in kilograms divided by height in meters squared.

Table 5. Baseline Characteristics of Propensity-Matched Groups

| Characteristics | No. (%) of Participants[a] | | P Value[b] |
	LRPR (n = 744)	HRPR (n = 248)	
Age, mean (SD), y	71.7 (10.9)	71.7 (11.3)	.43
Age ≥75 y	343 (45)	127 (51)	.16
Male	559 (75)	191 (77)	.55
Smokers	147 (20)	48 (19)	.89
Hypercholesterolemia	398 (53)	134 (54)	.88
Diabetes mellitus	199 (27)	70 (28)	.65
Hypertension	442 (59)	151 (61)	.68
Previous PCI	145 (19)	47 (19)	.85
Previous myocardial infarction	204 (27)	70 (28)	.81
Previous coronary surgery	49 (7)	16 (6)	.94
3-Vessel disease	243 (33)	82 (33)	.91
LVEF <40%	284 (38)	97 (39)	.79
Killip class III-IV	41 (6)	15 (6)	.75
ST-elevation acute myocardial infarction	254 (34)	82 (33)	.76

Abbreviations: HRPR, high residual platelet reactivity; LRPR, low residual platelet reactivity; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
[a] Data are expressed as No. (%) of participants unless otherwise indicated.
[b] The χ^2 test was used for comparison of categorical variables and the unpaired 2-tailed t test for continuous variables.

has no effect on in vitro tests after the loading dose of 600 mg of clopidogrel.

Other studies using light transmittance aggregometry with a different dose of ADP and a lower cutoff or other methods report a higher incidence of high residual platelet reactivity, with a resulting lower positive predictive value of the test.[5,10,11,16] In the GRAVITAS trial, which reported an incidence of 40.7% high platelet reactivity after clopidogrel loading, the observational comparison of patients with and without high on-treatment reactivity as assessed by VerifyNow (Accumetrics, San Diego, California) showed an increased number of ischemic events in the former group, but the difference did not reach statistical significance.[16]

Platelet aggregation functional test–driven antiplatelet treatment enhancement using an increased dose of clopidogrel or a switch to ticlopidine may result in an ADP test result of less than 70% in approximately 60% of patients without an effect on clinical outcome. This finding is consistent with the results of the GRAVITAS trial, the first concluded large-scale study assessing the clinical impact of doubling a long-term dosage of clopidogrel in PCI patients with high residual platelet reactivity after clopidogrel loading.[16] In the GRAVITAS trial, which enrolled mainly patients with stable coronary artery disease, the increased maintenance dosage of clopidogrel (150 mg) was associated with a modest but significant reduction in platelet reactivity as assessed by VerifyNow, but this in vitro effect was not associated with a reduction in the rate of ischemic events compared with patients receiving a standard (75-mg) maintenance dosage of the drug. Previous smaller studies of adjusted therapy under the guidance of in vitro tests have shown that adjunctive clopidogrel reloading or use of glycoprotein IIb/IIIa inhibitors may be beneficial. However, these studies focused only on short-term clinical events.[17-20]

To our knowledge, this is the first study to explore the association of high residual platelet reactivity after clopidogrel loading with long-term clinical outcome in patients with ACS undergoing an invasive procedure. Acute coronary syndromes have been associated with a diminished platelet response to clopidogrel with spontaneous decrement of platelet reactivity after the early period of ACS and intervention.[21,22] In this study, the landmark

analysis for the primary end point and cardiac death using a prespecified starting point at 6 months after the index procedure shows that the prognostic strength of a single measurement of residual platelet reactivity during ACS is maintained at long-term follow-up. This finding supports the hypothesis that high residual platelet reactivity after 600-mg clopidogrel loading is an independent prognostic marker of short- and long-term ischemic events.

Consistent with previous studies, our study shows that high residual platelet reactivity is likely to be associated with a worse patient risk profile. However, after adjusting for differences in baseline characteristics between low and high residual platelet reactivity groups, high residual platelet reactivity remained an independent predictor of cardiac death.

Our study must be evaluated in light of some limitations. First, the data derive from a prospective nonrandomized registry. We used propensity score matching to make the patient groups comparable according to the measured confounders. However, residual unmeasured confounding cannot be excluded. Second, despite the difference in stent thrombosis rates between groups, the study was not powered for this adverse event. Third, it is unknown if nonantiplatelet drugs and adherence to recommended drugs may have influenced the long-term outcome. Fourth, this study adjusted antiplatelet therapy using an increased maintenance dosage of clopidogrel or ticlopidine. It is unknown if high residual platelet reactivity after 600-mg clopidogrel loading in patients undergoing PCI for ACS is a nonmodifiable risk factor for thrombotic events or if tailored therapy with use of new antithrombotic agents such as prasugrel or ticagrelor, which provide more potent and predictable in vitro platelet aggregation inhibition, have a positive effect on clinical outcome.[23-25] Thus, the results of this study should be considered only as hypothesis generating for further studies of tailored therapy using new antithrombotic agents.

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