Post-Treatment Platelet Reactivity Predicts Long-Term Adverse Events Better Than the Response to Clopidogrel in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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Introduction and objectives: Poor response to antiplatelet therapy has been associated with adverse long-term outcomes. The objective of this study is to assess the relationship between response to clopidogrel and post-treatment platelet reactivity (PPR) and 1-year major adverse cardiovascular events (MACE) in patients with non-ST segment elevation acute coronary syndrome (NSTEACS).

Methods: Patients with NSTEACS undergoing early coronary angiography were enrolled in this prospective, observational study. The VerifyNow® analyzer was used to measure clopidogrel response and PPR immediately before coronary angiography.

Results: Of the 179 patients included (97 percutaneous coronary intervention, 21 coronary artery bypass graft), 161 (90%) completed 1-year follow-up and 18 (11%) incurred MACE: 10 deaths, 6 myocardial infarctions, 2 strokes, 5 revascularizations. Lower response to clopidogrel (31±21% vs. 43±21%; *P*=.049) and higher PPR (204±60 vs. 155±67 platelet reaction units [PRU]; p=.006) were significantly associated with MACE occurrence. Multivariate analysis confirmed PPR (OR per 10-unit increase, 1.12, 95% CI, 1.01-1.24; *P*=.020) as an independent predictor of MACE. A PPR cut-off value of 175 PRU was associated with an adjusted OR for 1-year MACE occurrence of 3.9 (95% CI, 1.2-15.4; *P*=.024).

Conclusions: PPR predicts adverse long-term outcomes better than response to clopidogrel in patients with NSTEACS. Patients with PPR values above 175 PRU were identified as being at higher risk for adverse long-term events.

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La reactividad plaquetaria postratamiento predice los eventos adversos a largo plazo mejor que la respuesta al clopidogrel en pacientes con síndrome coronario agudo sin elevación del ST

Introducción y objetivos. Una peor respuesta al tratamiento antiagregante está relacionada con la recurrencia de eventos clínicos. El objetivo de este estudio es valorar la relación entre la respuesta al clopidogrel y la reactividad plaquetaria postratamiento (RPP) con la recurrencia de eventos adversos cardiovasculares a 1 año en pacientes con síndrome coronario agudo sin elevación del ST (SCASEST).

Métodos. Estudio observacional, prospectivo de la respuesta al clopidogrel y RPP (analizador VerifyNow®) inmediatamente antes de la coronariografía diagnóstica.

Resultados. De 179 pacientes incluidos (97 con intervencionismo coronario y 21 con cirugía coronaria), 161 (90%) completaron seguimiento a 1 año y 18 (11%) sufrieron eventos: 10 muertes, 6 infartos agudos de miocardio no fatales, 2 accidentes cerebrovasculares y 5 nuevas revascularizaciones. Una peor respuesta al clopidogrel (31% ± 21% frente a 43% ± 21%; p = 0,049) y una mayor RPP (204 ± 60 frente a 155 ± 67 unidades de reactividad plaquetaria [URP]; p = 0,006) se asociaron significativamente con la aparición de eventos. El análisis multivariable confirmó la RPP (*odds ratio* [OR] por incremento de 10 URP = 1,12; intervalo de confianza [IC] del 95%, 1,01-1,24; p = 0,020) como predictor independiente de eventos adversos cardiovasculares mayores. Un punto de corte de RRP de 175 URP se asoció con OR ajustada = 3,9 (IC del 95%, 1,2-15,4; p = 0,024) para la aparición de eventos.

Conclusiones. La RPP predice la aparición de eventos adversos a largo plazo mejor que la respuesta al clopidogrel en pacientes con SCASEST. Los pacientes con valores de RPP > 175 URP presentan mayor riesgo de sufrir eventos adversos.

Palabras clave: *Inhibidores de la agregación plaquetaria. Síndrome coronario agudo. Eventos adversos cardiovasculares mayores.*

ABBREVIATIONS

MACE: major adverse cardiovascular events
NSTEACS: non-ST-segment elevation acute coronary syndrome
IPA: inhibition of platelet aggregation
PCI: percutaneous coronary intervention
PPR: post-treatment platelet reactivity
PRU: platelet reaction units

INTRODUCTION

Dual antiplatelet therapy with aspirin and clopidogrel is the therapy of choice for decreasing the incidence of major adverse cardiovascular events (MACE) in patients with non-ST-elevation acute coronary syndrome (NSTEACS),[1,2] particularly those undergoin a percutaneous coronary intervention (PCI).[3] However, the therapeutic response to aspirin,[4,5] clopidogrel,[5-7] or both agents[8,9] varies considerably.

Poor response to clopidogrel, defined as lower inhibition of platelet aggregation (IPA), is related to MACE occurring at short-term[10] and long-term.[11] Elevated post-treatment platelet reactivity (PPR) values have been used to identify patients with NSTEACS who have undergone PCI and are at greater risk of MACE at 30 days.[12] Some authors advocate that PPR is a better estimate of atherothrombotic risk than IPA analysis,[10,12-18] because IPA fails to consider final absolute platelet reactivity.

Most of these studies have been conducted with optical aggregometry, a method too labor-intensive for routine clinical practice. Rapid platelet-function analyzers, such as the VerifyNow® system (Accumetrics Inc., San Diego, California, USA),[19-22] make this analysis more useful in clinical practice.

The purpose of this study is to determine the relationship between recurrence of MACE at 1 year and the response to clopidogrel and PPR results in patients with NSTEACS, using the VerifyNow® analyzer.

METHODS

Patient Screening and Procedures

A prospective observational study was conducted, including patients with NSTEACS who underwent early diagnostic coronary angiography at our hospital. NSTEACS was defined as typical prolonged chest pain at rest (>20 min) with ST-segment changes or T-wave abnormalities in the electrocardiogram, or troponin-T levels ≥0.03 g/L. At admission, the patients received a loading dose of clopidogrel 300 mg followed by 75 mg/d and a loading dose of aspirin 250 mg followed by 100 mg/d. The main exclusion criteria were long-term oral anticoagulant therapy, contraindication or allergy to aspirin, clopidogrel, or heparin, active treatment with glycoprotein IIb-IIIa inhibitors before diagnostic coronary angiography, active bleeding, and thrombocytopenia (<100 000/mL). The study was approved by our hospital's ethics committee and all patients gave written informed consent to participate. Antithrombotic therapy and abciximab, in the case of PCI, were prescribed according to our hospital's protocol in accordance with clinical practice guidelines. At discharge, patients received aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for 9 months (clopidogrel therapy at 75 mg/d was extended to 12 months in patients who received a drug-eluting stent). The patients who underwent coronary artery bypass grafting (CABG) discontinued clopidogrel at least 5 days prior to surgery.

Platelet Function Assessment

A blood sample was obtained through the arterial introducer (discarding the first 10 mL) for platelet aggregation analysis before the diagnostic coronary angiography began. The samples (2 mL) were placed in tubes with 3.2% sodium citrate (Vacuette®, Greiner Bio-One, Monroe, North Carolina, USA) and platelet aggregation was measured with the VerifyNow® analyzer (Accumetrics Inc., San Diego, California) within 1 hour of sample collection. The technical details of this system have been previously described.[23] The VerifyNow® system is based on an interaction between the platelet receptors and the fibrinogen-coated beads that induce aggregation. Light absorption by the sample is measured as a function of time, and the rate of aggregation is measured in platelet reaction units (PRU). There is an excellent correlation between the results obtained with this system and those obtained with optical aggregometry.[20,21]

Only a P2Y12-specific kit is needed to determine the effect of clopidogrel. Platelet reactivity unrelated

to the effect of thienopyridines (baseline reactivity) is measured with the first channel; the PPR remaining after inhibition of the clopidogrel-mediated P2Y12 receptor is then measured with the second channel (values expressed in PRU). Clopidogrel response is calculated as follows:

[1 – (PPR in PRU / baseline reactivity in PRU)]×100

Events

The primary endpoint of the study was 1-year MACE: death from any cause, nonfatal acute myocardial infarction, new revascularization (CABG or PCI) after readmission for NSTEACS, and ischemic stroke. Nonfatal acute myocardial infarction was defined as the appearance of ischemic symptoms lasting more than 20 minutes plus pathological Q-waves in at least 2 contiguous electrocardiographic leads or elevated creatine kinase-MB fraction (creatine kinase-MB) and troponin-T in at least 2 measurements. Stroke was defined as a new focal neurologic deficit assessed by diagnostic computed tomography and confirmed by a neurologist. Additional endpoints were the individual components of the primary endpoint. Bleeding was classified according to the Thrombolysis In Myocardial Infarction (TIMI) classification.[24] Minor bleeding was defined as clinically manifest bleeding accompanied by a decrease of 3 to 5 g/dL in hemoglobin or 9% to <15% in hematocrit. Major bleeding was defined as a >5 g/dL decrease in hemoglobin or ≥15% in hematocrit. Patients were contacted by telephone 1, 6, and 12 months after the procedure to identify those who had experienced a MACE, in which case the medical history or a report from the attending physician was reviewed.

Statistical Methods

The study was designed to test the hypothesis that the incidence of the primary endpoint is related to a higher PPR and/or a lower IPA. The PPR and IPA values are expressed as continuous variables and in quartiles; the discrete variables, in absolute numbers and percentages; and the continuous variables, as the mean (SD) or median (interquartile range). We assessed the differences between groups using the χ^2 test or Fisher's exact test for discrete variables. A linear regression analysis was performed to assess differences in the continuous variables. Event-free survival was analyzed using the Kaplan-Meier method and the differences were assessed by the log-rank test. Receiver operating characteristic (ROC) curves were used to analyze the sensitivity and specificity of the platelet function variables for detecting the incidence of MACE. The sample size was calculated from the results of the CURE and CREDO studies.[1,2] Thus, if we assume a 10.5% incidence of the primary endpoint, a poor clopidogrel response of 30%,[25] and a 10% loss to follow-up to detect a difference of 0.25 with a power of 80% and $P<.05$, then the calculated sample size should be ≥175 patients. To identify factors correlated with PPR and the percentage of IPA, univariate and multivariate analyses were performed using a general linear model with PPR and IPA as continuous variables. Multivariate logistic regression models were constructed with the primary endpoint as a dependent variable. The multivariate stepwise forward logistic regression models included all variables (demographic, clinical, and angiographic) that had shown an association with PPR, percentage of IPA, or MACE with a probability value of $P\leq.20$ in the univariate models. A P value (2-tail) ≤.05 was considered statistically significant. The statistical analyses were performed using JMP 6 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient Characteristics, Clinical Events, and Platelet Function

A total of 179 patients with NSTEACS were included between January 2005 and February 2006: 97 (54%) patients underwent coronary angioplasty and 21 (12%), CABG. Telephone contact was made with 161 (90%) at 1, 6, and 12 months, a period during which 18 (11%) patients experienced MACE: 10 deaths (9 of cardiovascular cause), 6 nonfatal acute myocardial infarctions, 2 strokes, and 5 new revascularizations after NSTEACS. Of the 18 patients who experienced MACE, 5 presented more than 1. Six minor and 2 major bleeding episodes were reported. The median time-to-event was 53 (range, 27-184) days. The demographic, clinical, and angiographic characteristics of the study population according to the ocurrence of MACE are summarized in Table 1.

The PPR and the percentage of IPA showed normal distributions, with mean values of 157 (68) PRU and 43% (21%), respectively (Figure 1). There was no significant association between IPA and the other variables analyzed. However, higher PPR was observed in patients previously treated with clopidogrel (191 [67] vs 155 [66] PRU; $P=.023$), TIMI risk score >3 (171 [69] vs 146 [64] PRU; $P=.028$) and LVEF <50% (189 [73] vs 152 [63]; $P=.01$).

TABLE 1. **Demographic, Clinical, and Angiographic Characteristics According to the Appearance of Major Cardiovascular Adverse Events on Long-Term Follow-up in the Complete Study Cohort**

Characteristic	Complete Cohort (n=161)	MACE (n=18)	No MACE (n=143)	*P*
Age, mean (SD), y	67.6 (1.9)	73.6 (7.1)	66.9 (1.9)	.001
Women	41 (25)	8 (44)	33 (23)	.049
Hypertension	95 (59)	17 (94)	78 (55)	.001
Diabetes under treatment	36 (27)	9 (50)	27 (19)	.006
Dyslipidemia	86 (53)	12 (67)	74 (52)	.231
Current smoker	30 (19)	0	30 (21)	.026
Platelets, 10^9/L	214.5 (71.9)	214.4 (66.7)	214.5 (69.7)	.995
Creatinine clearance, mL/min	75 (29)	51 (28)	78 (29)	.016
Prior antiplatelet therapy	63 (39)	13 (72)	50 (35)	.004
Prior clopidogrel therapy	22 (14)	8 (44)	14 (10)	.001
Duration of clopidogrel treatment, h	69 (30)	68 (30)	81 (29)	.105
Prior myocardial infarction	34 (21)	9 (50)	25 (17)	.002
History of PCI	20 (12)	5 (28)	15 (10)	.036
History of CABG	12 (7)	4 (22)	8 (6)	.031
LVEF <50%	30 (19)	5 (28)	25 (17)	.516
Beta-blockers	116 (72)	10 (56)	106 (75)	.099
ACE inhibitors	116 (72)	13 (72)	103 (72)	.999
Nitrates	101 (63)	14 (78)	87 (61)	.161
Statins	135 (84)	18 (100)	117 (82)	.078
Preangiography troponin-T >0.1 µg/L	108 (67)	14 (82)	94 (66)	.272
TIMI risk score >3	88 (55)	15 (83)	73 (51)	.011
Extension of coronary artery disease				
No significant lesions	26 (16)	0	26 (18)	.077
Left main coronary artery disease	3 (2)	0	3 (2)	.389
Multivessel disease	87 (54)	13 (72)	74 (52)	.100
Number of diseased vessels	1.7 (1.1)	2.3 (.9)	1.6 (1.1)	.008
Postangiography treatment				
Medical treatment	52 (32)	8 (44)	44 (31)	.281
CABG	17 (11)	1 (6)	16 (11)	.696
Incomplete revascularization[a]	2 (12)	0	2 (12)	1
Mammary artery graft[a]	17 (100)	1 (100)	16 (100)	1
PCI	92 (57)	9 (50)	83 (58)	.615
Incomplete revascularization[a]	30 (33)	5 (55)	25 (30)	.039
Drug-eluting stent[a]	47 (51)	5 (55)	42 (51)	.289

ACE inhibitors indicates angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.
[a]Percentage calculated as the number of events/number of patients treated by PCI or CABG.
Data are expressed as mean (SD) or n (%).

Relationship Between Platelet Aggregation and Clinical Events

A lower IPA (31% [21%] vs 43% [21%]; *P*=.049) was related to the appearance of MACE: odds ratio (OR) per 10-unit increase of 1.34 (95% confidence interval [CI], 1.03-1.8). A higher PPR (204 [60] vs 155 [67] PRU; *P*=.006) was related to 1-year MACE: OR per 10-unit increase (95% CI, 1.03-1.23) (Table 2). Neither IPA nor PPR were significantly associated with bleeding. In patients who underwent coronary angioplasty, the results for the overall study population were consistent: a lower IPA (28% [15%] vs 45% [22%]; *P*=.03) and a higher PPR (212 [71] vs 151 [69] PRU; *P*=.02) were associated with the appearance of MACE.

A multivariate logistic regression analysis was performed, including all variables associated with the appearance of MACE with a *P* value <.20 (Table 1). The independent predictors of MACE at 1 year were PPR (10-unit increase in PPR is associated with adjusted OR [AOR], 1.12; 95% CI, 1.01-1.24; *P*=.02) and previous platelet therapy (AOR, 4.56; 95% CI, 1.13-23; *P*=.033). IPA was not an independent predictor in this model. To determine the effect of adjusting for this variable, 2 new multivariate analysis models were constructed using the above variables: one in which PPR was excluded, in which IPA was found not to be an independent predictor, and one in which IPA was excluded, in where PPR maintained statistical significance (AOR, 1.2; 95% CI, 1-1.4; *P*=.002). None of the cases were excluded

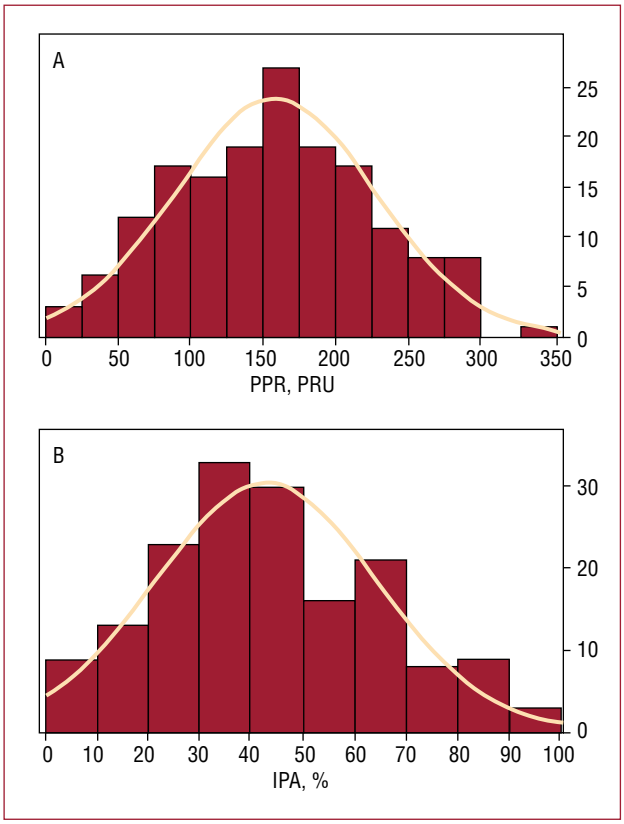

Figure 1. Normal distribution of A: post-treatment reactivity platelet (PPR) and B: inhibition of platelet aggregation (IPA). PRU indicates platelet reaction units.

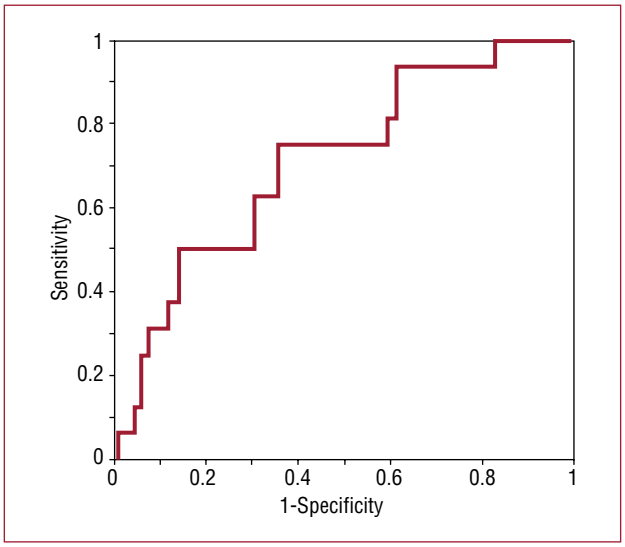

Figure 3. Receiver operating characteristic curve (ROC): post-treatment platelet reactivity (PPR) values by discriminating against the appearance of major adverse cardiovascular events (MACE). PRU indicates platelet reaction units.

from these models because of a lack of information on the variables studied.

The incidence of MACE was significantly higher (P=.009) among patients in the quartiles with higher PPR values (Figure 2). The ROC curve (Figure 3) had a low area under the curve (0.71); when the PPR threshold was assumed to be 175 PRU, it had a sensitivity of 75% and a specificity of 64% for predicting the appearance of MACE. The positive and negative predictive values were 20% and 96%, respectively. Figure 4 shows that patients with PPR values above the 175-PRU cut-off had a lower event-free survival rate. Table 3 shows the demographic, clinical, and angiographic characteristics, separated according to values below and above the PPR cut-off of 175 PRU. Following adjustment for co-

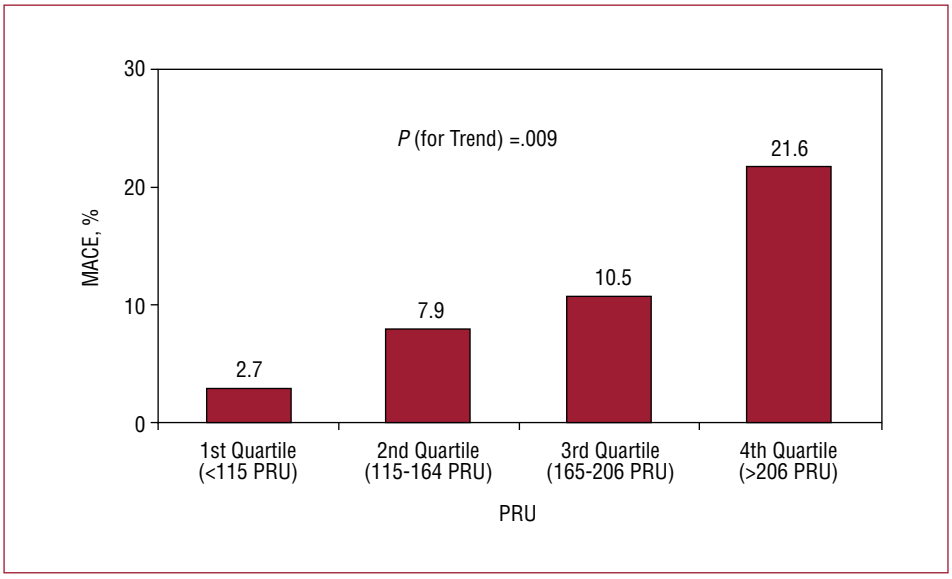

Figure 2. Major adverse cardiovascular events (MACE) at 1 year, separated into quartiles of post-treatment platelet reactivity (PPR) measured in platelet reaction units (PRU).

TABLE 2. **Major Adverse Cardiovascular Events and Other Clinical Events During Follow-up, Separated According to Post-Treatment Platelet Reactivity Values, and Platelet Aggregation Inhibition in Complete Study Cohort**

Events	PPR (PRU)	*P*	IPA, %	*P*
Total MACE (n=18)	204 (60)		31 (21)	
		.006		.049
No MACE (n=143)	155 (67)		43 (21)	
Deaths (n=10)	197 (55)		36 (19)	
		.072		.33
Survivors (n=151)	158 (68)		42 (22)	
Nonfatal AMI (n=6)	196 (61)		25 (26)	
		.25		.21
No nonfatal AMI (n=155)	159 (68)		42 (21)	
Revascularization (n=5)	237 (88)		30 (25)	
		.26		.50
No revascularization (n=156)	159 (67)		42 (21)	
Stroke (n=2)	225 (80)		47 (10)	
		.33		.80
No stroke (n=159)	160 (68)		42 (21)	
Major bleeding (n=2)	119 (156)		64 (47)	
		.39		.14
No major bleeding (n=159)	161 (67)		42 (21)	
Minor bleeding (n=6)	139 (50)		46 (18)	
		.43		.61
No minor bleeding (n=155)	161 (68)		42 (22)	

AMI indicates acute myocardial infarction; MACE, major adverse cardiovascular events; (IPA) inhibition of platelet aggregation; PPR, post-treatment platelet reactivity; PRU, platelet reaction units.
Data are expressed as mean (SD).

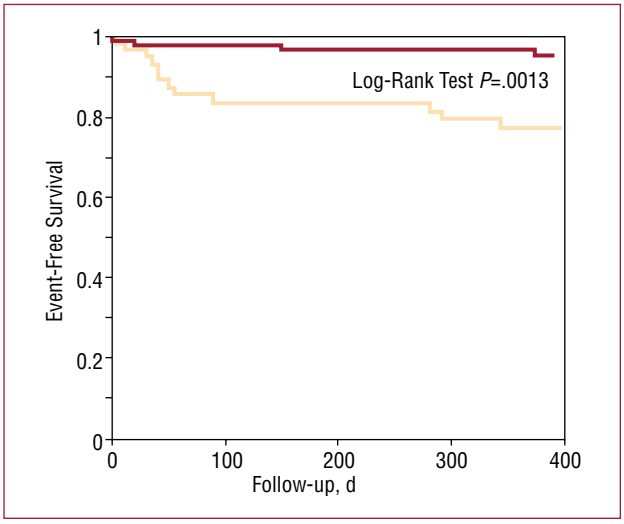

Figure 4. Event-free Kaplan-Meier survival curves for patients according to post-treatment platelet reactivity values above (continuous line) and below (discontinuous line) the cut-off of 175 platelet reaction units (PRU).

variables, only PPR >175 PRU (OR, 3.9; 95% CI, 1.2-15.4; *P*=.024) and prior clopidogrel therapy (OR, 5.4; 95% CI, 1.6-18.9; P=.007) were associated with the appearance of MACE at 1 year.

DISCUSSION

Our results show that high PPR and low IPA before diagnostic coronary angiography are significantly related to the appearance of MACE in patients with NSTEACS. In addition, the multivariate regression analysis adjusted for other variables showed that PPR predicts the appearance of MACE better than IPA.

Previous studies have related the degree of IPA and PPR to the recurrence of adverse events.[10-12,16-18] Our study corroborates this relationship over a 1-year follow-up period in a high-risk population: patients with NSTEACS and a significant rate of long-term antiplatelet therapy (39%). Various studies[11,12] have shown a relationship between PPR and MACE recurrence at short-term. Cuisset et al[12] described an association between PPR and 30-day MACE in patients with NSTEACS; regardless of clopidogrel loading dose (300 vs 600 mg), a persistently high PPR was the only variable significantly associated with MACE recurrence (OR, 13.82; *P*<.0001). Higher PPR has also been related to long-term MACE: Bliden et al[16] described this association in a 1-year follow-up study after coronary angioplasty (75% for stable angina), and Angiolillo

TABLE 3. **Demographic, Clinical, and Angiographic Characteristics and Major Cardiovascular Adverse Events According to Post-Treatment Platelet Reactivity Above and Below the Cutoff of 175 Platelet Reaction Units**

Characteristic	PPR ≤175 PRU (n=97)	PPR >175 PRU (n=64)	*P*
Age, mean (SD), y	66.9 (1.5)	69 (1.8)	.216
Women	22 (23)	19 (30)	.361
Hypertension	57 (59)	38 (60)	.786
Diabetes under treatment	20 (21)	16 (25)	.430
Dyslipidemia	53 (55)	33 (52)	.893
Current smoker	22 (23)	8 (13)	.128
Platelets, 10^9/L	215.2 (71.2)	214.4 (69.8)	.946
Creatinine clearance, mL/min	76 (30)	75 (30)	.804
Prior antiplatelet therapy	34 (35)	29 (45)	.176
Prior clopidogrel therapy	9 (9)	13 (20)	.028
Duration of clopidogrel treatment, h	67 (30)	75 (31)	.088
Prior myocardial infarction	17 (19)	16 (27)	.259
History of PCI	11 (11)	9 (14)	.623
History of CABG	7 (7)	5 (8)	.902
LVEF <50%	14 (14)	16 (25)	.099
Beta-blockers	71 (73)	45 (70)	.285
ACE inhibitors	70 (72)	46 (72)	.737
Nitrates	60 (62)	41 (64)	.675
Statins	83 (86)	52 (81)	.204
Preangiography troponin-T >0.1 µg/L	63 (65)	45 (70)	.431
TIMI risk score >3	44 (45)	44 (69)	.012
Extension of coronary disease			
No significant lesions	19 (20)	7 (11)	.139
Left main coronary disease	1 (1)	2 (3)	.347
Multivessel disease	36 (60)	46 (51)	.284
Number of diseased vessels	1.5 (1)	1.9 (1.1)	.056
Postangiography treatment			
Medical treatment	31 (32)	21 (33)	.885
CABG	9 (9)	8 (12)	.531
Incomplete revascularization[a]	1 (6)	1 (6)	1
Mammary artery graft[a]	9 (53)	8 (47)	1
PCI	57 (59)	35 (55)	.787
Incomplete revascularization[a]	16 (28)	12 (34)	.640
Drug-eluting stent[a]	31 (54)	16 (46)	.193
MACE at 1 year of follow-up	5 (5)	13 (20)	.003

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; PPR, post-treatment platelet reactivity; PRU, platelet reaction units.
*Percentage calculated as the number of events/number of patients treated by PCI or CABG.
Data are expressed as mean (SD) or n (%).

et al[17] in a 2-year follow-up of stable diabetic patients.

Some of the earlier studies included both stable and unstable patients; however, Geisler et al[26] have shown that patients with acute coronary syndrome present higher PPR than patients with stable angina.

In our study population, patients who experienced MACE presented poorer baseline and clinical characteristics. These factors could contribute to a proinflammatory and prothrombotic state and, therefore, to greater platelet reactivity. However, the multivariate regression analysis, once adjusted for these variables, confirmed PPR as an independent predictor of MACE, as previously described.[10,12-18] In our study, a 10-unit increase in PPR was associated with an AOR for 1-year MACE of 1.12 (95% CI, 1.01-1.24; *P*=.02). The EXCELSIOR study[10] showed that a 10% increase in platelet aggregation was associated with an AOR for 30-day MACE of 1.32 (95% CI, 1.04-1.61; *P*=.026). In addition, the 1-year

incidence of MACE was significantly higher in the quartiles with higher PPR values.

No consensus currently exists regarding the cut-off point to identify patients with poor response to clopidogrel; moreover, clopidogrel response (percentage decrease in IPA) does not take absolute pre-treatment and post-treatment platelet reactivity into account.[27] In our study, an analysis of the ROC curve identified a PPR value of 175 PRU as the best discriminatory value for predicting MACE recurrence. In addition, a PPR >175 PRU was associated with an AOR for MACE of 3.9 (95% CI, 1.2-15.4; *P*=.024). Except for development of a MACE, previous clopidogrel therapy, and TIMI risk score >3, no differences were found in the demographic, clinical, or angiographic characteristics when comparing patients with PPR below and above the cut-off described. In patients who underwent coronary angioplasty with a drug-eluting stent, Price et al[18] established a PPR cut-off of ≥235 PRU (using the VerifyNow® analyzer) to identify patients at a higher risk of experiencing adverse events at 6 months; the differences between the cut-off obtained in our study and the cut-off found by Price et al[18] may be due to a longer antiplatelet/antithrombotic treatment period before platelet function was assessed in our group and to population differences.

Of note, the multivariate regression analysis showed that previous antiplatelet therapy is an independent predictor of MACE recurrence. Likewise, a higher number of patients with PPR above the 175-PRU cut-off were previously under clopidogrel therapy. Bliden et al[16] reported that patients on long-term clopidogrel therapy scheduled for coronary intervention who presented higher PPR values had an increased risk of recurrence of ischemic events.

Study Limitations

The use of clopidogrel loading doses of 300 mg (following the recommendations approved at the start of the study) could be considered a limitation because loading doses ≥600 mg are related to higher IPA.[10-12,28-30] However, this difference becomes less relevant because of the extended time between the clopidogrel loading dose and coronary angiography (69.4 [30.2] h), which was never less than 6 h; thus, the drug had reached stable levels in most patients. Compliance with the clopidogrel therapy prescribed may have had some influence on the outcome, particularly in medically managed patients.

Some methodological limitations should be mentioned. Because of the exploratory nature and the limited power of our study, the results should be validated in larger cohorts. Second, the inclusion of too many variables in the multivariate analyses may have led to models that hinder interpretation, and lastly, 10% of all patients included were lost to follow-up, which could affect the results obtained.

Clinical Implications

Platelet reactivity measurement in patients with NSTEACS is clinically relevant with regard to the appearance of MACE over the long term. Patients under previous clopidogrel treatment who experience an acute coronary syndrome are at higher thrombotic risk, and more intensive therapeutic strategies should be investigated in this group. In patients with a high PPR, different therapeutic options could reduce MACE recurrence. These options could include using higher maintenance doses of clopidogrel (150 mg/d),[31,32] repeating the loading dose,[33,34] or using direct thrombin inhibitors or glycoprotein IIb-IIIa inhibitors. Furthermore, new, more potent P2Y12 receptor antagonists are currently under investigation in various clinical trials. Bonello et al[35] have recently demonstrated the safety of a clopidogrel reloading strategy until adequate IPA is reached, as well as its efficacy in reducing adverse events.

CONCLUSIONS

In patients with NSTEACS, the PPR predicts the recurrence of cardiovascular adverse events over the long term better than clopidogrel response. Our study population represents all "real-world" patients and the results reinforce the predictive value of PPR. Larger clinical studies are needed to determine if a decrease in PPR would result in a significant improvement of the recurrence of long-term events.

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