ORIGINAL ARTICLE

Association between Mean Platelet Volume and Resistance to Aspirin and P2Y12 Receptor Inhibitors in Elderly Patients with Acute Coronary Syndrome

Asociación entre el volumen plaquetario medio y la resistencia a aspirina e inhibidores del receptor p2y12 en pacientes ancianos con síndrome coronario agudo

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ABSTRACT

Background: Antiplatelet resistance and mean platelet volume (MPV) are event predictors in acute coronary syndrome (ACS), but their association has been poorly studied.
Objective: The aim of this study was to evaluate the association between MPV and resistance to aspirin (ASA) and P2Y12 receptor inhibitors (P2Y12i) in elderly patients with ACS.
Methods: Patients over 65 years old diagnosed with ACS were included in the study. They were divided into group 1 (resistance to both antiplatelet agents), group 2 (resistance to one antiplatelet agent) and group 3 (no resistance to antiplatelet agents). Platelet aggregation was measured between 12 and 24 hours postloading (by light transmission aggregometry). Resistance to P2Y12i was considered as maximum percentage of aggregation (MPA) with adenosine diphosphate (ADP) >60% and resistance to ASA as MPA with arachidonic acid (ARA) >20%. The composite endpoint of global death and cardiovascular re-hospitalization was considered during follow-up.
Results: One hundred and ninety five patients included in the study received ASA and P2Y12i (120 received clopidogrel and 75 ticagrelor). Nineteen percent of patients belonged to group 1, 34.4% to group 2 and 46.6% to group 3. Mean platelet volume was associated with resistance to both antiplatelet agents [OR 1.02 (95% CI 1.01-1.05), p=0.03], while MPV and the GRACE score were independent predictors of the composite endpoint [HR 1.03 (95% CI 1.01-1.07), p=0.04, and HR 1.02 (95% CI 1.01-1.04), p=0.02, respectively].
Conclusions: Mean platelet volume was associated with the presence of resistance to both antiplatelet agents. During follow-up, MPV and the GRACE score were predictors of the composite endpoint.

Key words: Acute coronary syndrome - Mean platelet volume - Platelet aggregation inhibitors - P2Y12 purinergic receptors

RESUMEN

Introducción: La resistencia a antiagregantes y el volumen plaquetario medio (VPM) son predictores de eventos en el síndrome coronario agudo (SCA). La asociación entre ambos ha sido poco estudiada.
Objetivos: Evaluar si existe asociación entre la resistencia a la aspirina (AAS) e inhibidores del receptor P2Y12 (iP2Y12) y el VPM en pacientes mayores de 65 años con SCA.
Material y métodos: Se incluyeron pacientes mayores de 65 años con diagnóstico de SCA. Se dividieron en: grupo 1 (resistencia a ambos antiagregantes), grupo 2 (a uno de los antiagregantes) y grupo 3 (a ningún antiagregante). Se midió la agregación plaquetaria entre las 12 y 24 horas poscarga (por light transmission aggregometry). Se consideró resistencia a iP2Y12 a un porcentaje máximo de agregación (PMA) con ADP > 60% y a la AAS a un PMA con ARA > 20%. En el seguimiento se consideró el punto final combinado de muerte global y reinternación cardiovascular.
Resultados: Se incluyeron 195 pacientes que recibieron AAS e iP2y12 (120 recibieron clopidogrel y 75 ticagrelor); grupo 1 (19%), grupo 2 (34,4%) y grupo 3 (46,6%). El VPM se asoció a la resistencia a ambos antiagregantes (OR 1,02 (IC 95% 1,01-1,05), p = 0,03. A su vez, el VPM y el GRACE fueron predictores independientes del punto combinado (HR 1,03 (IC 95% 1,01-1,07), p = 0,04 y HR 1,02 (IC 95% 1,01-1,04), p = 0,02), respectivamente.
Conclusiones: El VPM se asoció a la presencia de resistencia a ambos antiagregantes. En el seguimiento el VPM y el score GRACE fueron predictores del punto combinado.

Palabras clave: Síndrome coronario agudo - Volumen plaquetario medio - Inhibidores de agregación plaquetaria - Receptores purinérgicos P2Y12

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INTRODUCTION

The main pathophysiological mechanism in the acute coronary syndrome (ACS) is activation, adhesion and subsequent platelet aggregation after plaque rupture (1-2). Double antiplatelet therapy with aspirin (ASA) and a P2Y12 receptor inhibitor (P2Y12i) has been shown to reduce thrombotic complications, becoming the core of ACS treatment (3-4). However, about one third of patients have increased platelet reactivity (IPR) despite antiplatelet treatment with ASA and/or clopidogrel. (5-6) Increased platelet reactivity has also been observed with ticagrelor (7) and prasugrel (8). This lack of inhibition of platelet activity in vitro, called resistance to antiplatelet agents, has been associated with an increased risk of thrombotic events. (6, 9, 10)

In turn, increased platelet reactivity is associated with an increase in platelet volume, (2) and higher levels of procoagulant factors and greater glycoprotein Ib and IIb/IIIa expression have been found in patients with increased mean platelet volume (MPV). (11, 12) Moreover, MPV is increased in patients with acute myocardial infarction compared with controls and has been a predictor of both mortality and other cardiovascular events in patients with ACS. (13, 14)

It has also been shown that MPV increases with age in patients with coronary heart disease. (15) The association between MPV and resistance to antiplatelet agents has been scarcely studied in elderly patients. The primary objective of this study was thus to evaluate whether there is an association between MPV and resistance to double antiplatelet therapy in patients over 65 years of age with ACS. A secondary objective was to evaluate whether these parameters are associated with events that occurred during follow-up.

METHODS

An observational, prospective, single center study, including patients over 65 years of age of age admitted to the coronary care unit with diagnosis of ACS, and who were treated with ASA and P2Y12i loading, was performed from January 2014 to July 2017. The exclusion criteria were the impossibility of measuring MPV or platelet aggregation within the required times and not receiving P2Y12i loading dose. Patients were divided into three groups according to the presence of antiplatelet resistance: group 1, with resistance to both antiplatelet agents; group 2, with resistance to one of the antiplatelet agents, and group 3, without resistance to antiplatelet agents.

Antiplatelet therapy

All patients were treated with ASA and P2Y12i loading dose on admission. The decision to use clopidogrel or ticagrelor, as well as loading doses of the antiplatelet agents, was made according to the criteria of the attending physician. The Institution's Cardiology service suggests following guideline recommendations for both non-ST-segment elevation ACS (3) and ST-segment elevation ACS. (4)

Blood sampling

In the admission laboratory, a hemogram with platelet count and MPV was performed on a vein blood sample anticoagulated with EDTA, using a Sysmex XT-2000i hematological counter.

In vitro platelet aggregation was performed between 12 and 24 hours after P2Y12i loading (clopidogrel or ticagrelor) and ASA. Samples were processed within 4 hours of collection using the light transmission aggregometry (LTA) method on an AggRAm aggregometer © (Helena Laboratories). The rationale for the method is to measure average platelet aggregation from the difference in optical density between platelet-rich plasma (PRP) and platelet-poor plasma (PPP) when an agonist is added. To evaluate platelet reactivity to ASA, arachidonic acid (ARA) was used at a concentration of 500 μg/ml, and adenosine diphosphate (ADP) at a concentration of 10 μM for P2Y12i. Resistance to P2Y12i was considered as maximum percentage of aggregation (MPA) with ADP >60% and to ASA as MPA with ARA >20%.

Follow-up

Follow-up for discharged patients was carried out by telephone contact or medical interview. A composite endpoint of all-cause death and cardiovascular rehospitalization (due to ACS, heart failure, arrhythmias and revascularization) was evaluated.

Statistical analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as percentage. Analysis of variance (ANOVA) was used to compare between the three groups of continuous variables when distribution was normal, and the Kruskal-Wallis test for non-normal distribution. The chi-square test was used to compare categorical variables.

To evaluate the association between MPV and antiplatelet resistance, univariate analysis was carried using group 1 as dependent variable (resistance to both antiplatelet agents) and MPV, as continuous variable, the GRACE score and other known variables associated with resistance such as serum creatinine, glycemia, leuko-glycemic index (L/G index), female gender, history of diabetes and dyslipidemia (7, 10) as independent variables. Subsequently, a multivariate analysis was performed using a logistic regression model, jointly analyzing the variables that were significant in the univariate analysis.

To establish the discriminating capacity of MPV and to predict the resistance to both antiplatelet agents, a Receiver Operating Characteristic (ROC) curve was built in order to determine the area under the ROC curve (AUC) and the cut-off point.

To analyze follow-up, univariate analysis was performed for the composite endpoint using MPV, the GRACE score and the L/G index as continuous variables and group 1 and use of clopidogrel as categorical variables. The variables that presented a significant association were analyzed in a multivariate model with the Cox regression method to establish the independent predictors of the composite endpoint, reporting the hazard ratio (HR) with the corresponding 95% confidence interval (95% CI). In addition, event-free survival was analyzed using Kaplan-Meier curves. Finally, the AUC was calculated to evaluate the discrimination capacity for the MPV composite endpoint. A value of $p < 0.05$ was considered significant. Statistix 7 software was used for the general analysis and Epidat 3.1 for the ROC curve.

Ethical considerations

The protocol was approved by the institutional Ethics Committee and the patients signed the informed consent.

RESULTS

Among a total of 287 patients admitted during the study period, 50 were excluded due to impossibility to perform any of the measurements and 42 for not having received P2Y12i loading dose. Finally, 195 patients (40 ST-segment elevation ACS and 155 non-ST-segment elevation ACS) were included. Mean age was 74±7 years and 43% were women. In 100% of cases, patients received ASA and P2Y12i loading dose (120 received clopidogrel and 75 ticagrelor). Aspirin dosing: 84.6% of patients (n=165) received 200 mg loading dose and the remaining patients 300 mg. Clopidogrel dosing: 76.1% (n=95) received 600 mg loading dose and 20.9% (n=25) 300 mg. All patients who received ticagrelor were administered 180 mg loading dose.

Nineteen percent (n=37) of the patients presented resistance to both antiplatelet agents (group 1); 34.4% (n=67) showed resistance to one of the agents (group 2) and 46.7% (n=91) showed no resistance to any antiplatelet agent (group 3). In group 2, the majority of patients showed resistance to ASA (n=50), while 17 patients showed resistance to P2Y12i (13 to clopidogrel and 4 to ticagrelor). In the entire population, the prevalence of resistance to ASA was 42.9%, to clopidogrel 36.6% and to ticagrelor 13.3%.

Table 1 shows baseline population characteristics. It is important to highlight that group 1 patients had higher MPV (10.9±0.3 vs. 10.6±0.4 vs. 10.2±0.5 fL, p=0.04), higher GRACE score (142±30 vs. 138±32 vs. 131±27, p=0.04) and greater use of clopidogrel

Table 1. Baseline population characteristics

	Group 1 (n=37)	Group 2 (n=67)	Group 3 (n=91)	p
Age (years)	74 ± 7	73 ± 7	72 ± 6	0.28
Female - n (%)	21 (56.7)	27 (40.2)	36 (39.5)	0.06
Hypertension - n (%)	31(83.7)	52 (77.6)	73 (80.2)	0.74
Diabetes - n (%)	12 (32.4)	16 (23.8)	24 (26.3)	0.7
Dyslipidemia - n (%)	19 (24.3)	38 (56.7)	54 (59.3)	0.7
Current smoker - n (%)	6 (16.2)	10 (14.9)	24 (26.3)	0.3
Previous infarction -n (%)	3 (8.1)	10 (14.9)	10 (10.9)	0.1
Previous PCI- n (%)	3 (8.1)	10 (14.9)	10 (10,9)	0.1
Previous CABGS - n (%)	2 (5.4)	12 (17.9)	10 (10.9)	0.15
General laboratory				
-Hct. (%)	37 ± 4	38± 4	38 ±5	0.65
-WC count (/ml)	8,787 ± 2,871	8,729 ± 3,600	7,800 ± 2,800	0.1
-Glycemia (mg/dl)	138 ± 38	134 ± 38	123 ± 34	0.08
-Leuko/glycemic index	1,287 ± 812	1,236 ± 1.000	951 ± 514	0.02
-Serum urea (mg/dl)	51 ± 26	44 ± 23	42 ± 18	0.37
-Serum creatinine (mg/dl)	1.03 ± 0.67	1.11 ± 0.62	1.03 ± 0.66	0.12
Platelets				
-Platelet count (x103/mm3)	216 ± 34	206 ± 54	204 ± 43	0.07
-MPV (fL)	10.9 ± 0.3	10.6 ± 0.4	10.2 ± 0.5	0.04
Platelet aggregation				
MPA with ARA (%)	48.3 ± 21.7	33.8 ± 18.2	16.8 ± 5.3	
MPA con ADP (%)	74.3 ± 6.5	53.1 ± 16.7	43.4 ± 14.4	
GRACE score	142 ± 30	138 ± 32	131 ± 27	0.04
Admission diagnosis				
-NSTEACS - n (%)	25 (67.5)	54 (80.6)	76 (83.5)	0.12
Antiplatelet treatment				
ASA- n (%)	37 (100)	67 (100)	91 (100)	
Clopidogrel - n (%)	31 (83.7)	41(61.2)	47 (51.6)	0.003
Ticagrelor - n (%)	6 (16.3)	26 (28.8)	44 (48.4)	0.003
Concomitant treatment				
Betablokers	30 (81)	58 (86.5)	78 (85.7)	0.49
Statins	34 (91.8)	62 (92.5)	84 (92.3)	0.54
ACEI o ARAII**	30 (54)	40 (59.7)	54 (59.3)	0.76
Omeprazol	1 (2.7)	3 (4.4)	2 (2.1)	0.23

PCI: Percutaneous coronary intervention. CABGS: Coronary artery bypass graft surgery. Hct: Hematocrit. WC: White cells. MPV: Mean platelet volume. MPA: Maximum percentage of aggregation. ARA: Arachidonic acid. ADP: Adenosine diphosphate. ACEI: Angiotensin converting enzyme inhibitors. ARAII: Angiotensin II receptor antagonists.

(83.7% vs. 61.2% vs. 51.6%, p=0.003) than those in groups 2 and 3. On the other hand, patients who presented resistance to an antiplatelet agent (groups 1 and 2) presented higher leuko-glycemic index (L/G index) than patients who did not present resistance (1,287±812 vs. 1,236±1.000 vs. 951±514, p=0.02).
Table 2 shows univariate and multivariate analysis for the presence of resistance to both antiplatelet agents. Mean platelet volume and treatment with clopidogrel were independent predictors of resistance to both antiplatelet agents (OR 1.02 (1.01-1.04), p=0.02) and (4.11 (1.62-10.4), p <0.01), respectively. The AUC for MPV was 0.62 (95% CI 0.51-0.72) and MPV>10.7 fL was established as cutoff point, with OR 2.71 (95% CI 1.25- 5.87), p=0.01, adjusted for treatment with clopidogrel (Figure 1).

Follow-up and events

Average follow-up was 259±170 days. The composite endpoint was found in 10.3% of patients (n=20), with mortality of 2.56% (n=5), and MPV and the GRACE score were independent predictors (HR 1.03 (95% CI 1.01-1.07), p=0.04 and HR 1.02 (95% CI 1.01-1.04), p=0.02), respectively (Table 3).

The AUC of MPV to predict the composite endpoint was 0.75 (95% CI 0.65-0.85) and a cutoff point of MPV >10.6 fL was established. In the analysis adjusted by the GRACE score, MPV >10.6 presented a HR of 3.82 (95% CI 1.20-7.31), p=0.01. Figure 2 shows the Kaplan-Meier curve of MPV >10.6 fL for the composite endpoint.

DISCUSSION

The main purpose of this study was to evaluate the association between MPV and the presence of resistance to ASA and P2Y12i (clopidogrel and ticagrelor) in patients over 65 years of age with ACS. We found that MPV is associated with the presence of IPR post ASA and P2Y12i loading and, in addition, it is an independent risk factor of resistance to both antiplatelet agents. However, the discrimination capacity of MPV to predict resistance to both antiplatelet agents was poor (AUC 0.61).

Our findings agree with the work of other authors.

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
MPV	1.03 (1.01-1.05)	0.02	1.02 (1.01-1.04)	0.02
Platelet count	1.00 (0.99-1.00)	0.3	--	
Glycemia	1.001 (0.99-1.01)	0.12	--	
Serum Creatinine	1.01 (1.00-1.03)	0.08	--	
L/G index	1.01 (1.00- 1.01)	0.12	--	
Female	2.17 (1.03-4.56)	0.04	2.01 (0.99-4.67)	0.08
GRACE score	1.01 (1.001-1.02)	0.04	1.00 (0.99-1.02)	0.12
Use of clopidogrel	4.51 (1.74-11.6)	<0.01	4.11 (1.62-10.4)	<0.01
Diabetes	1.31 (0.62-2.77)	0.48	--	
Dyslipidemia	0.76 (0.37-1.55)	0.44	--	

OR: Odds ratio. MPV: Mean platelet volume. L/G index: Leuko-glycemic index.

Table 2. Factors associated with resistance to both antiplatelet agents: univariate and multivariate analysis

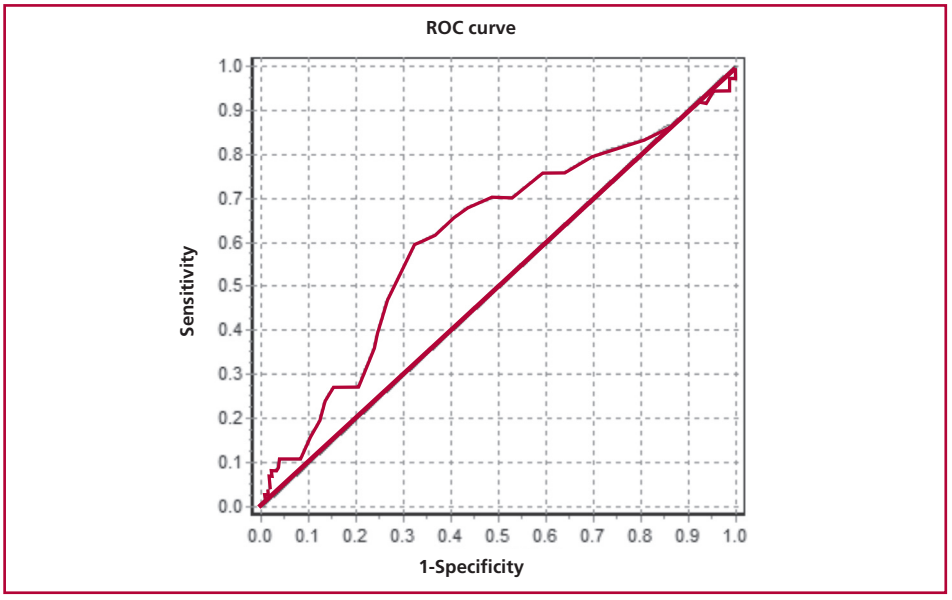
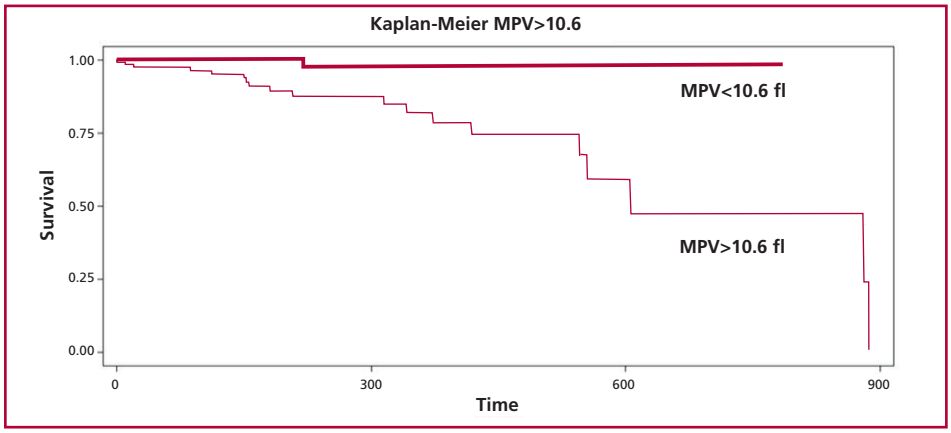


Fig. 1. ROC curve. MPV to predict resistance to both antiplatelet agents. A cutoff point for MPV >10.6 fl. was established (OR 2.71 (95% CI 1.25-5.87), p=0.01).

Table 3. Univariate and multivariate analysis for the composite endpoint

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
MPV	1.05 (1.02-1.10)	0.03	1.03 (1.01-1.07)	0.04
GRACE score	1.03 (1.01-1.09)	0.03	1.02 (1.01-1.04)	0.02
Group 1	2.10 (1.08-3.95)	0.04	1.23 (0.98-2.43)	0.3
L/G index	1.00 (0.98-1.07)	0.08	--	
Use of clopidogrel	0.89 (0.65-1.83)	0.7	--	

Fig. 2. Kaplan-Meier curve. MPV >10,6 fL for the composite endpoint



Uzel et al. (16) evaluated the relationship between the response to clopidogrel and MPV in 185 patients hospitalized with ACS and found that MPV was a predictor of IPR with a moderate discrimination capacity (AUC 0.70). In this sense, Jakl et al. (17) presented similar results in 190 patients with ACS, where MPV was associated with resistance to double antiplatelet therapy (ASA and clopidogrel).

In a control case study that evaluated patients undergoing angioplasty after ACS with and without early intrastent thrombosis, (18) MPV was associated with IPR in both groups. Choi et al. (19) presented similar findings in 208 patients undergoing angioplasty after ACS. This association was also found in patients with stable angina. (20) These studies present some differences with the present work. Our patients were older (the average age of the studies presented does not exceed 68 years) and moreover, none of the studies cited used ticagrelor, while, in our population, 38% of patients was treated with that drug.

In a recent study Verdoia et al. (21) found no significant association between MPV and resistance to ASA, clopidogrel, or ticagrelor in 487 patients followed-up after an ACS.

An important difference with the mentioned works is the time in which the measurements were made. In most cases, aggregation was measured between 3 and 5 days after treatment initiation, while in the Verdoia study aggregation was evaluated after one month.

We assessed afterload platelet reactivity between 12 and 24 hours after the loading dose, similarly to other authors. (22, 23) We used the LTA method, which has been classically used to measure platelet activity. (5, 24) The mentioned studies have used other methods developed more recently –as the VerifyNow®- that have been validated and used in numerous works. (23, 24)

We found that more than half of the patients showed resistance to at least an antiplatelet agent. Approximately 42% showed resistance to ASA, 34% to clopidogrel and 13% to ticagrelor. Previously, very variable rates of resistance have been reported, ranging between 5% and 57% for ASA (25), 4% and 68% (24) for clopidogrel and, 3% and 13% for ticagrelor (7, 26)

Numerous studies have reported that the presence of IPR is associated with an increased risk of cardiovascular events. (9, 24) In this work, resistance to both antiplatelet agents was associated with the presence of the composite endpoint in the univariate analysis, while the multivariate analysis was canceled by MPV and the GRACE score. In this sense, a meta-analysis that included more than 26,000 patients found that after adjusting for confounders, IPR was not significantly associated with an increased risk of events. (27) In addition, randomized large-scale studies could not demonstrate that platelet reactivity-guided treatment resulted in reduced events. (22, 28)

Finally, MPV was an independent predictor of the composite endpoint, with an acceptable discrimination power (AUC 0.75). Our group has reported the prognostic value of MPV events in elderly patients with ACS. (14) These results are in agreement with the findings of numerous studies. (13, 29) In addition, the fact that it is measured in the routine complete blood count and does not generate an additional cost,

makes it attractive as a marker of cardiovascular events during follow-up.

This work is added to the series of studies that show a relationship between MPV and antiplatelet agent resistance. It has been observed that larger platelets have a higher level of thromboxane A2 per unit, higher expression of GP IIb-IIIa receptors and greater presence of reticulated platelets than small platelets. (11, 12, 28, 30) This could partly explain this association. However, the fact that MPV and not antiplatelet agent resistance is independently associated with the risk of events shows that the pathophysiological mechanism by which MPV is a risk factor is not yet elucidated.

Limitations

This is a small study, carried out in a single center that exclusively assists elderly patients (it is an effector of the National Institute of Social Services for Retirees and Pensioners, PAMI- Argentina). Although platelet reactivity was measured with the classic LTA method, it requires that the processing is done within 4 hours of blood withdrawal, which resulted in the non-inclusion of many patients.

CONCLUSIONS

In the population studied, the presence of resistance to ASA and P2Y12i was high. Mean platelet volume was associated with the presence of resistance to both antiplatelet agents. At follow-up, MPV and the GRACE score, but not the presence of resistance to antiplatelet agents, were predictors of the composite endpoint.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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