The effect of acetylsalicylic acid resistance on prognosis of patients who have developed acute coronary syndrome during acetylsalicylic acid therapy

Gultekin F Hobikoglu MD¹, Tugrul Norgaz MD¹, Huseyin Aksu MD¹, Orhan Ozer MD¹, Mehmet Erturk MD¹, Evren Destegul MD¹, Umit Akyuz MD², Sennur Unal Dai MD¹, Ahmet Narin MD¹

GF Hobikoglu, T Norgaz, H Aksu, et al. The effect of acetylsalicylic acid resistance on prognosis of patients who have developed acute coronary syndrome during acetylsalicylic acid therapy. *Can J Cardiol* 2007;23(3):201-206.

AIM: The relationships between clinical events and acetylsalicylic acid resistance (AR), as well as its frequency, have been established in stable patients with coronary artery disease (CAD). Although acute coronary syndrome (ACS) patients taking acetylsalicylic acid have been accepted as a high-risk population, the role of AR has not been investigated in these patient groups. Thus, in the present study, the impact of AR was investigated in patients with ACS who were taking acetylsalicylic acid.

METHODS: Between January 2001 and February 2003, 140 ACS patients were included in the present prospective study. All patients had ACS while taking acetylsalicylic acid. Coronary angiographic scores for severity and extent of CAD were determined for all patients. The effect of acetylsalicylic acid on platelet function was assessed by the platelet function analyzer PFA-100 (Dade Behring, USA). The primary end point was the composite of death, myocardial infarction, cerebrovascular accident and revascularization. The mean follow-up period was 20 months.

RESULTS: Patients with AR were older than patients without AR (63.8±10.8 years versus 58.3±11.2 years; $P=0.005$). Moreover, myocardial damage was higher in patients with AR according to cardiac troponin T values (1.11±1.3 µg/L versus 0.41±0.5 µg/L; $P=0.01$). The composite end point of death, myocardial infarction, cerebrovascular accident or revascularization was present in 16 of 45 patients (35%) with AR and in 13 of 79 patients (16%) without AR (hazard ratio 2.46, 95% CI 1.18 to 5.13; $P=0.016$). After adjustment for age, platelet count, cardiac troponin T value and CAD severity score, AR remained an independent predictor for long-term adverse events (hazard ratio 3.03, 95% CI 1.06 to 8.62; $P=0.038$).

CONCLUSIONS: The clinical event rate was found to be higher in ACS patients with AR than in those without AR. Thus, it may be concluded that there is a strong correlation between a worse prognosis and AR in these patients.

Key Words: Acetylsalicylic acid resistance; Acute coronary syndrome; Prognosis

The central role of platelet activation and aggregation in the pathophysiology of acute coronary syndrome (ACS) has been well documented through serological (1-3), angiographic (4) and autopsy (5) studies. Early trials with unstable angina patients have demonstrated that acetylsalicylic acid decreases the risk of death or myocardial infarction (MI) by 50% compared with placebo (6). The second International

L'effet de la résistance à l'acide acétylsalicylique sur le pronostic des patients ayant développé un syndrome coronarien aigu pendant un traitement à l'acide acétylsalicylique

OBJECTIF : On a établi les liens entre les événements cliniques et la résistance à l'acide acétylsalicylique (RA), de même que la fréquence de ces événements, chez des patients stables atteints d'une coronaropathie. Bien que les patients atteints d'un syndrome coronarien aigu (SCA) qui prenaient de l'acide acétylsalicylique aient été acceptés au sein de la population très vulnérable, on n'a pas évalué le rôle de la RA auprès d'eux. On a toutefois évalué les répercussions de la RA chez les patients atteints d'un SCA qui prenaient de l'acide acétylsalicylique.

MÉTHODOLOGIE : Entre janvier 2001 et février 2003, 140 patients atteints d'un SCA ont été inclus dans la présente étude prospective. Tous les patients souffraient de SCA pendant qu'ils prenaient de l'acide acétylsalicylique. On a établi l'indice de coronarographie en matière de gravité et d'étendue de la coronarographie chez tous les patients. On a évalué l'effet de l'acide acétylsalicylique sur la fonction plaquettaire au moyen de l'analyseur de fonction plaquettaire PFA-100 (Dade Behring, États-Unis). La valeur de seuil primaire correspondait au composite de décès, d'infarctus du myocarde, d'accident vasculaire cérébral (AVC) et de revascularisation. Le suivi moyen était de 20 mois.

RÉSULTATS : Les patients ayant une RA étaient plus âgés que ceux sans RA (63,8±10,8 ans par rapport à 58,3±11,2 ans; $p = 0,005$). De plus, les lésions myocardiques étaient plus importantes chez les patients ayant une RA d'après les valeurs T de troponine cardiaque (1,11±1,3 µg/L par rapport à 0,41±0,5 µg/L; $p = 0,01$). Seize des 45 patients (35 %) ayant une RA atteignaient la valeur de seuil composite de décès, d'infarctus du myocarde, d'AVC ou de revascularisation, par rapport à 13 des 79 patients (16 %) sans RA (rapport de risque instantané [RRI] 2,46, 95 % IC 1,18 à 5,13; $p = 0,016$). Après rajustement compte tenu de l'âge, de la numération plaquettaire, de la valeur T de troponine cardiaque et de l'indice de gravité du SCA, la RA demeurait un prédicteur indépendant de l'issue indésirable à long terme (RRI 3,03, 95 % IC 1,06 à 8,62; $p = 0,038$).

CONCLUSIONS : Le taux d'événements cliniques était plus élevé chez les patients atteints d'un SCA avec une RA que chez ceux sans RA. Ainsi, on peut conclure qu'il existe une forte corrélation entre un pronostic plus négatif et la RA chez ces patients.

Study of Infarct Survival (ISIS-2 [7]) has confirmed the critical role of acetylsalicylic acid in the treatment of acute MI by showing a nearly 20% decrease in mortality compared with acetylsalicylic acid used alone. Despite the clear benefit of acetylsalicylic acid in patients with coronary artery disease (CAD), acetylsalicylic acid has been shown to manifest variable antiplatelet activity in individual patients. Previous studies

¹Siyami Ersek Thorax and Cardiovascular Surgery Center, Department of Cardiology; ²Haydarpaşa Numune Hospital, Department of Internal Medicine, Istanbul, Turkey

Correspondence: Dr Gultekin F Hobikoglu, Sedef sokak Onur Sitesi blok 7 daire 19 Kosuyolu, Uskudar, Istanbul, Turkey.

Telephone 90-216-65718999, fax 90-216-450-0270, e-mail ghobikoglu@hotmail.com

Received for publication June 28, 2006. Accepted November 19, 2006

(8-13) have estimated that 5% to 45% of the population does not achieve an adequate antiplatelet effect by using acetylsalicylic acid. Although the appropriate method for detecting acetylsalicylic acid resistance (AR) is still controversial and the absolute definition is still lacking (14,15), the concept of AR has been greatly emphasized in medical literature (16). Many possible mechanisms for development of AR have been proposed. These can be summarized as follows: insufficient dosing (17), polymorphism of glycoprotein IIIa (18,19), production of prostaglandin H₂ in monocytic and endothelial cells through the cyclo-oxygenase-2 pathway (20), elevated levels of cyclo-oxygenase-2 as a result of increased platelet degradation (21) and increased platelet sensitivity to ADP (22).

Patients with ACS who have been identified as high risk include those who present with acute ischemia despite chronic acetylsalicylic acid therapy. This group represents an increasing proportion of patients, and their subsequent rate of death or MI is 50% higher than that of those who have not previously taken acetylsalicylic acid (23). Patients who have an acute coronary event during acetylsalicylic acid therapy may be at a higher risk for subsequent events due to several reasons. Previous acetylsalicylic acid use may simply act as a marker for a more extensive or aggressive cardiovascular disease. Alternatively, the worse outcomes observed in patients previously treated with acetylsalicylic acid may result from unmeasured hematological factors or endothelial dysfunction. A third possibility is that patients who develop ACS during acetylsalicylic acid therapy may be acetylsalicylic acid-resistant, with relative or complete intrinsic resistance against the effects of acetylsalicylic acid.

In these patients, the relationship between worse prognosis and AR is not clear. The current prospective study evaluated the clinical and angiographic findings of ACS in acetylsalicylic acid-resistant and acetylsalicylic acid-sensitive patients, and assessed the relationship between AR and prognosis.

METHODS

Patients

Between January 2001 and February 2003, 524 patients were admitted to the emergency department and hospitalized with the diagnosis of non-ST-elevation ACS. Among them, 140 patients who had been using acetylsalicylic acid for at least the previous seven days were prospectively included in the present study. We had previously reported (24) the frequency of AR in patients with ACS in a study that also included some of the same patients from the present study.

The present study was reviewed and approved by the ethical committee at the Siyami Ersek Thoracic and Cardiovascular Surgery Center, Istanbul, Turkey. All participants gave informed consent before enrolment.

Exclusion criteria included the following: the ingestion of ticlopidine, clopidogrel, dipyridamole or other nonsteroidal anti-inflammatory drugs; the use of other drugs containing acetylsalicylic acid; administration of heparin or low-molecular-weight heparin 24 h before enrolment; a major surgical procedure performed one week before enrolment; malignant paraproteinemias; a family or personal history of a bleeding disorder; a platelet count of less than $150 \times 10^9/L$ or higher than $450 \times 10^9/L$; a hemoglobin concentration of less than 80 g/L; a history of myeloproliferative disorders; and a history of heparin-induced thrombocytopenia.

Fasting blood samples were taken into 7.5% EDTA, and hematological parameters (hemoglobin concentration, mean platelet volume, as well as platelet, and red and white blood cell counts) were measured using an autoanalyzer (Gen S, Coulter Corporation, USA). Moreover, serum values of cardiac markers, including cardiac troponin T (cTnT), creatine kinase-myocardial band (CK-MB), urea, creatinine and glucose were measured. Cardiovascular risk factors were identified through patient interviews.

The following risk factors were assessed: current smoking status, hypertension (patients using antihypertensive drugs or those with known and untreated hypertension), diabetes mellitus (patients using insulin or an oral hypoglycemic agent), a family history of premature CAD and hypercholesterolemia (patients using cholesterol-lowering drugs, or having a low-density lipoprotein cholesterol level higher than 3.36 mmol/L or a total cholesterol level of higher than 5.17 mmol/L).

Detection of AR

Blood samples were obtained on admission by venipuncture with an 18-gauge needle; samples were drawn into 4.5 mL vacutainer tubes anticoagulated with 3.8% sodium citrate. The vacutainer tubes were filled to capacity and gently inverted three to five times to ensure complete mixing of the anticoagulant. Platelet function analyses were performed within 1 h.

The effect of acetylsalicylic acid on platelet function was assessed using the platelet function analyzer PFA-100 (Dade Behring, USA), which simulates primary hemostasis in the injured blood vessel. The PFA-100 uses disposable test cartridges that have collagen-coated membranes infused with either ADP or epinephrine. The analyzer aspirates whole blood at a high shear rate through the capillary, where it comes into contact with the membrane; platelets then adhere to the membrane surface and start to aggregate. A platelet plug forms on occlusion of the aperture and cessation of blood flow. The closure time (CT) reflects specific platelet function for the sample evaluated. With the help of the PFA-100, platelet dysfunction caused by acetylsalicylic acid may be detected by a prolonged CT with the collagen/epinephrine (C/E) cartridge, and a normal CT (less than 114 s) with the collagen/ADP cartridge (25). The normal CT and the cut-off values were detected using samples of 30 healthy volunteers with matching features, in terms of age and sex, who had not been using acetylsalicylic acid. The mean + 2 SD C/E CT of the group was accepted as the cut-off value for AR. AR was defined by the PFA-100 as having a normal C/E CT (below the control group cut-off value) despite acetylsalicylic acid treatment.

Coronary angiography

Selective coronary angiography was applied by the femoral approach using Judkin's technique. Multiple views were obtained for all patients, with the left anterior descending and left circumflex coronary arteries visualized in at least four different views, and the right coronary artery imaged in at least two different views using cineangiographic equipment (Philips Integris H3000, Philips Medical Systems, Netherlands). Coronary angiograms were recorded on CDs in the Digital Imaging and Communications in Medicine format, and were scored according to the following techniques:

- Vessel score: the number of vessels with a significant stenosis (50% or greater reduction in lumen diameter). The degree of stenosis was defined as the greatest percentage of reduction in luminal diameter in any view

compared with the nearest normal segment, which was determined visually. Scores ranged from 0 to 3, depending on the vessels involved. Left main artery stenosis was scored as single-vessel disease.

- Severity score: the Gensini score, which has been described previously (26). In brief, the coronary arterial tree was divided into segments with multiplying factors according to the functional importance of any given segment (five points for the left main trunk and one-half point for the most distal segments), and the percentage of reduction in lumen diameter of each narrowing was assigned a score (0, 1, 2, 4, 8, 16 or 32, according to the degree of stenosis). The sum of the scores of all segments results in the Gensini score, which attributes emphasis to the severity of the disease.
- Negri extent score (27): any segment with evidence of atherosclerosis receives one point for the left main coronary artery, the whole left anterior descending artery, as well as the proximal parts of the circumflex and right coronary arteries, and one-half point for the other segments. The sum of the score gives indexes on CAD extent.

The scores were determined by one of the investigators (TN or GH), who had no knowledge of the presence of AR.

Study end points

The primary end point was the composite of death, MI, cerebrovascular accident (CVA) and revascularization, and secondary end points included the individual events of death, MI, CVA and revascularization. Death was defined as all-cause mortality due to MI, ischemic CVA, and other vascular and nonvascular causes. MI was defined as the presence of at least two of the following criteria: prolonged angina (longer than 30 min); total creatine kinase elevation (more than two times the upper limit of normal as confirmed by CK-MB fraction isoenzyme elevation); electrocardiographic evidence of infarction; ST-segment elevation of at least 0.1 mV (measured 0.2 s after the J point) in two contiguous leads; or new significant Q wave more than 0.04 s in duration or having a depth of greater than one-quarter of the corresponding R wave amplitude, or both. CVA was defined as a focal neurological deficit compatible with signs or symptoms persisting for longer than 24 h, and was classified as hemorrhagic or nonhemorrhagic according to the results of computerized tomography or magnetic resonance imaging. Revascularization was defined by percutaneous transluminal coronary angiography or coronary artery bypass graft surgery done for reinfarction, angina at rest or with minimal exertion, or ischemia on physiological testing after the initial revascularization or hospitalization.

Follow-up

Follow-up was performed by telephone interview with all patients enrolled between January 2001 and February 2003, regardless of AR status. Those people performing the follow-up interviews were blinded for acetylsalicylic acid sensitivity status. For those patients who had reached at least one primary end point, recorded data and medical reports were evaluated to determine whether they met the inclusion criteria. Follow-up via telephone was complete in 124 patients or family members.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD in the text and tables. Categorical variables are presented as frequencies and percentages. Unpaired Student's *t* test for continuous variables and χ^2 test for categorical variables were performed to compare patient groups. Event-free survival analysis was performed using Kaplan-Meier curves. Log-rank tests were used for screening univariable group results with respect to outcomes. Univariate predictors with $P < 0.05$ were included in a stepwise multivariable Cox regression model. The selection method was a forward selection with a significance level of $P = 0.05$ for entering an explanatory variable into the model. The final model only included significant variables with $P < 0.05$ using the Wald test. Variables entered into the model included age, platelet count, CAD severity score and AR. SPSS 10.0 for Windows (SPSS Inc, USA) was used for the entire statistical work-up. $P < 0.05$ was considered statistically significant.

RESULTS

The control group showed a C/E CT of 131.8 ± 18.8 s using the PFA-100. The cut-off value obtained for C/E CT was 169.4 s using the data of control group. AR was defined as a C/E CT of less than 170 s despite taking acetylsalicylic acid, and in the study group, 53 patients (37.8%) were found to have AR by this definition. The mean value of the C/E CT was 125.8 s (range 52 s to 169 s) in patients with AR and 231.5 s (range 171 s to 296 s) in patients without AR; no closure had taken place (more than 300 s) in 30 patients of the latter group.

Patients were taking acetylsalicylic acid at doses of 100 mg or 300 mg daily. Nineteen per cent of patients with AR (11 of 47; mean acetylsalicylic acid dose 262 ± 79 mg) were taking acetylsalicylic acid at 100 mg daily, and this percentage for patients with AR was 15.1% (13 of 73; mean acetylsalicylic acid dose 269 ± 72 mg) ($P = 0.6$).

Clinical patient features are shown in Table 1. Patients with AR were older than those without AR (63.8 ± 10.8 years versus 58.3 ± 11.2 years; $P = 0.005$). The frequency of non-ST-elevation MI was 51% in patients (27 of 53) with AR and 37% in patients (32 of 87) without AR. Patients with AR had the tendency to have a non-ST-elevation MI more often, but this difference was not statistically significant ($P = 0.08$). Moreover, myocardial damage was higher in patients with AR according to the cTnT value (1.11 ± 1.3 $\mu\text{g/L}$ versus 0.41 ± 0.5 $\mu\text{g/L}$; $P = 0.01$ [Figure 1]).

Coronary angiography was performed in all patients before hospital discharge. On coronary angiography, the vessel score (2.3 ± 0.8 versus 2.1 ± 0.9 ; $P = 0.21$), severity scores (61.4 ± 32.4 versus 51.0 ± 36.2 ; $P = 0.24$), extent scores (5.8 ± 2.3 versus 5.7 ± 3.1 ; $P = 0.90$) and revascularization rates (40% versus 39%, $P = 0.72$) were not different between patients with or without AR, respectively. Prehospital and follow-up period medications were not different between groups ($P > 0.05$) (Table 1). According to the follow-up visits, all patients continued on 100 mg acetylsalicylic acid, and none of them discontinued treatment.

One hundred twenty-four of the 140 patients (88%) completed the follow-up period. Complete follow-up was achieved in 45 of 53 patients with AR (85%) and in 79 of 87 patients without AR (91%). The mean follow-up period was 20 months (range 18 to 24 months). During the 20-month follow-up period, major events occurred (death, MI, CVA or revascularization) in 16 of 45 (35.5%) patients with AR and in 13 of 79 (16.4%) patients without AR (χ^2 $P = 0.016$).

TABLE 1
Characteristics of patients with (+) and without (–) acetylsalicylic acid resistance (AR)

	AR+ (n=45)	AR– (n=79)	P
Age, years (mean ± SD)	63.8±10.8	58.3±11.2	0.005
Female, n (%)	16 (35)	19 (24)	0.33
Smoking, n (%)	22 (49)	31 (39)	0.41
Hypertension, n (%)	19 (42)	42 (53)	0.37
Diabetes mellitus, n (%)	7 (15)	16 (20)	0.52
Hypercholesterolemia, n (%)	23 (51)	28 (35)	0.19
Prior PCI, n (%)	14 (31)	36 (45)	0.25
Prior CABG, n (%)	5 (11)	11 (14)	0.61
Laboratory values, mean ± SD			
Hemoglobin (g/L)	133±12	135±13	0.66
Platelet count (×10 ⁹ /L)	231.8±57.4	238.6±59.2	0.27
Mean platelet volume (fL)	8.4±1.1	8.2±1.0	0.24
Angiographic scores, mean ± SD			
Vessel score	2.3±0.8	2.1±0.9	0.27
Severity score	61.4±32.4	51.0±36.2	0.23
Extent score	5.8±2.3	5.7±3.1	0.94
Revascularization, n (%)	18 (40)	31 (39)	0.74
PCI	6 (13)	12 (16)	0.21
CABG	12 (27)	18 (23)	0.10
Medications used at baseline, n (%)			
Beta-blockers	18 (40)	29 (37)	0.33
ACE inhibitors	15 (33)	27 (34)	0.82
Statins	18 (40)	31 (39)	0.76
Medications used during follow-up, n (%)			
Beta-blockers	38 (84)	67 (85)	0.90
ACE inhibitors	18 (40)	38 (48)	0.17
Statins	33 (73)	59 (75)	0.78
Ticlopidine/clopidogrel	6 (13)	11 (14)	0.93

ACE Angiotensin-converting enzyme; CABG Coronary artery bypass grafting; PCI Percutaneous coronary intervention

Figure 2 shows the Kaplan-Meier curves for event-free survival based on AR with log-rank test results (log-rank $P=0.016$, hazard ratio [HR] 2.46, [95% CI 1.18 to 5.13]). After adjusting for age, platelet count, cTnT value and CAD severity score, AR remained an independent predictor for long-term adverse events (HR 3.03, 95% CI 1.06 to 8.62; $P=0.038$). Moreover, we observed an association between AR and MI. The presence of AR was associated with a threefold increase in the risk of MI (HR 3.02, 95% CI 1.15 to 7.95; $P=0.02$). Association between AR and other adverse individual outcomes (CVA, revascularization and death) did not reach statistical significance (Table 2).

DISCUSSION

The present prospective study showed that clinical events occur more frequently in patients with AR who develop ACS while undergoing chronic treatment with acetylsalicylic acid. Although there are an increasing number of studies about AR in literature, a few have investigated the relation between clinical events and AR. In stable CAD patients, Gum et al (28) reported that during follow-up, AR was found to be associated with an increased risk of death, MI or CVA compared with patients who were acetylsalicylic acid-sensitive (24% versus

Figure 1 Cardiac troponin T (cTnT) values of patients with (+) and without (–) acetylsalicylic acid resistance (AR)

Figure 2 Kaplan-Meier curve in patients with (+) and without (–) acetylsalicylic acid resistance (AR)

10%, HR 3.12, 95% CI 1.10 to 8.90; $P=0.03$). In a subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study (29), urine levels of 11-dehydro-thromboxane B_2 , a metabolite of thromboxane A_2 , were measured in patients taking acetylsalicylic acid, and patients were followed up for five years. It was reported that high levels of urinary 11-dehydro-thromboxane B_2 were predictive of MI and cardiovascular death: the upper quartile had a twofold increased risk of MI and 3.5-fold increased risk of cardiovascular death compared with the lowest quartile. Higher levels of urinary thromboxane A_2 metabolites in these patients are more likely to be an indicator of the lack of the desired acetylsalicylic acid effect due to insufficient dosing, lack of patient compliance or AR.

The relation between AR and prognosis of ACS was evaluated in only one study (30), and recurrent cardiovascular events were found to be higher in patients with AR. In the present study, we also compared the demographic and clinical features of patients with AR with those of patients without AR, and

evaluated the effects of angiographic severity of CAD on prognosis. The reasons given in the previous studies for the increased risk in patients with ACS on acetylsalicylic acid therapy included older age and the presence of more severe CAD in these patients. According to our results, clinical events were less frequent in patients without AR, although they experience CAD as severe as patients with AR. These findings suggest that AR may be the reason of worse outcomes in acetylsalicylic acid users. If patients who experience recurrent events despite taking acetylsalicylic acid are resistant to its antiplatelet effects, those patients may benefit from the addition of other potent and effective antiplatelet therapies. This suggestion regarding such a preferential effect has been reported in three trials (23,31,32). In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial (23), patients who had undergone acetylsalicylic acid therapy had a significantly higher incidence of 30-day death or MI than patients who had not used acetylsalicylic acid before presentation (16.1% versus 13.0%, OR 1.3, 95% CI 1.1 to 1.5), and 63% of patients who had used acetylsalicylic acid previously had a significant 16% reduction in 30-day death or nonfatal MI when taking the glycoprotein IIb/IIIa inhibitor eptifibatide (17.3% versus 14.9%, OR 0.84). Patients who had not used acetylsalicylic acid previously, however, did not manifest a significant reduction in death or MI with eptifibatide (12.9% versus 13.0%, OR 1.02). In the Platelet Receptor Inhibition for Ischemic Syndrome Management in patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial (31) of the glycoprotein IIb/IIIa inhibitor tirofiban that included patients with non-ST-elevation ACS, similar findings were observed with worse outcomes in prior acetylsalicylic acid users. Also in this trial, a treatment effect was limited to prior acetylsalicylic acid users. In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial (32), in which one-third of patients were prior acetylsalicylic acid users, a reduction was observed in cardiovascular death and nonfatal MI when clopidogrel was added to standard therapies. However, resistance to clopidogrel has also been reported (33-35). Moreover, a recent study (36) has suggested that, as a group, patients with AR have a reduced response to clopidogrel.

Limitations

We recruited patients according to their history of acetylsalicylic acid use, but we did not measure the blood salicylate or serum/plasma thromboxane A₂ metabolite levels.

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TABLE 2

Hazard ratios for both univariate and multivariate analyses for acetylsalicylic acid resistance

	Hazard ratio (95% CI)	P
Univariate analyses		
Death, myocardial infarction, CVA and revascularization	2.32 (1.06–5.10)	0.03
Death	2.30 (0.77–6.85)	0.13
Myocardial infarction	3.02 (1.15–7.95)	0.02
CVA	1.63 (0.72–3.65)	0.23
Revascularization	1.07 (0.51–2.24)	0.84
Multivariate analyses		
Acetylsalicylic acid resistance	3.03 (1.06–8.62)	0.03
Severity score	1.01 (0.99–1.03)	0.65
Platelet count	0.98 (0.97–0.99)	0.007
Age	0.96 (0.90–1.02)	0.22
Cardiac troponin T value	0.68 (0.27–1.72)	0.68

CVA Cerebrovascular accident

We detected AR using the PFA-100 and did not compare it using an aggregometer. An aggregometer uses platelet-rich plasma, but the PFA-100 uses whole blood and simulates primary homeostasis, which is a better physiological approach to evaluate platelet function. The most appropriate method for detecting AR is still controversial, and an absolute definition is required. Furthermore, clinical reliability of this test was confirmed by the PFA-100, with worse outcomes in patients with an insufficient response to acetylsalicylic acid occurring during the follow-up period.

CONCLUSION

Because clinical events occur more frequently in patients with AR who develop ACS while under chronic treatment with acetylsalicylic acid, it can be concluded that a strong relationship exists between AR and poorer prognosis in this group of patients. The presence of AR, as detected by the PFA-100, was associated with a threefold increase in the risk of developing clinical events during a long-term follow-up; thus AR testing seems to be a reliable tool for clinical practice. Evaluating the presence of AR in these patients and adding different antiplatelet drugs for patients who have AR may improve in clinical outcomes.

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