Resistance to Clopidogrel: Prevalence and Associate Variables

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Abstract

Background: The dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel is the cornerstone of treatment for patients undergoing angioplasty with coronary stent implantation. However, some of these patients, despite the use of aspirin and clopidogrel, are not effectively anti-aggregated, a phenomenon known as resistance to antiplatelet agents. Its prevalence, as well as the conditions associated with it, is unknown in our country.

Objective: To determine the prevalence of clopidogrel resistance, as well as variables associated with it.

Methods: Patients admitted for elective angioplasty in chronic use of ASA and clopidogrel between January 2007 and January 2010 were studied. One hour after the procedure, platelet aggregation was measured using optical aggregometry with adenosine diphosphate 5 mmoles / l as agonist. At that moment, in a cross-sectional cohort, we determined the prevalence of clopidogrel resistance, defined as the value of platelet aggregation ≥ 43% and a logistic regression model to the variables associated with it.

Results: A total of 205 patients were analyzed (66.4 ± 11 years, 61.5% males). The prevalence of clopidogrel resistance was 38.5% (95% CI: 31.9 - 45.2%). Blood glucose (OR = 1.014; 95%CI: 1.004 - 1.023), previous myocardial infarction (OR = 2.320; 95%CI: 1.1103 - 4.892) and therapeutic response to ASA (OR = 1.057; 95%CI: 1.017 - 1.099) were the variables independently associated with clopidogrel resistance.

Conclusion: The prevalence of clopidogrel resistance was high. Glycemia, acute myocardial infarction and response to ASA were variables associated with it. A better understanding of this phenomenon is necessary considering the new antiplatelet aggregant agents. (Arq Bras Cardiol 2012;99(6):1135-1141)

Keywords: Platelet aggregation inhibitors; drug resistance; stents; coronary disease; angioplasty, balloon, coronary.

Introduction

Dual antiplatelet therapy with aspirin and thienopyridines is a cornerstone in the treatment of patients undergoing coronary stent implantation[1]. Although it was the drug initially used in combination with aspirin, ticlopidine[2] was quickly replaced by clopidogrel due to its better safety and tolerability profile[3]. Thus, currently, in spite of new antiplatelet agents, aspirin (81 to 300 mg/day)[4] and clopidogrel (75 mg/day) is the most widely used regimen after coronary stent implantation.

For some years, it has been known that the antiaggregant response of clopidogrel varies individually according to a number of factors such as genetics[4], drug interactions[5,6] and clinical conditions such as diabetes[7]. The incapacity of clopidogrel to inhibit platelet aggregation measured at the laboratory is known as clopidogrel resistance[8]. Regardless of the reasons for resistance, the prognostic impact of this condition has been shown in four meta-analyses[9-12].

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Manuscript received January 31, 2012; manuscript revised February 10, 2012; accepted August 1, 2012.

Despite the prognostic importance and growing scientific interest, according to our knowledge, there are no national publications that have described the occurrence of clopidogrel resistance.

The objective of this study is to determine the prevalence and conditions related to this phenomenon in patients undergoing elective coronary angioplasty with stent implantation, pretreated with aspirin and clopidogrel.

Material and Methods

This was a cross-sectional retrospective cohort study of patients admitted for elective angioplasty in the period between January 2007 and January 2010. Inclusion criteria were use of aspirin and clopidogrel for a period ≥ 5 days (self-reported), hospitalization on the day of angioplasty, angiographic success[1] and platelet aggregation measurement in the first hour after angioplasty. Patients using oral anticoagulants or any other antiaggregant drugs, those using glycoprotein IIB/IIIA inhibitors during angioplasty, those with platelet count <100,000 cells/mm^3 and hematocrit < 30% were excluded.

As part of an institutional protocol, patients within the first hour after angioplasty were submitted to blood sampling for assessment of platelet aggregation, blood glucose, hematocrit,

platelets, and creatinine levels. Platelet function was quantified by the optical aggregometry method in platelet-rich plasma (PRP) using the four-channel aggregometer Chronolog ® 470VS (Chronolog, Havertown, PA, USA). This method is still currently the most widely used in studies of clopidogrel resistance, and in spite of more recent assessment methods of platelet function, still remains the gold standard[13]. Adenosine diphosphate (ADP) was used as agonist to measure the therapeutic effect of clopidogrel at a concentration of 5 mmoles/L (Chronolog, Havertown, PA, USA). The pre-analytical and analytical phases followed all international recommendations for measuring platelet aggregation (PA)[14].

Individuals with PA value ≥ 43% were considered resistant to clopidogrel[15]. The following variables were analyzed: a) clinical-demographic: age, sex, ethnicity, comorbidities (hypertension, diabetes mellitus, dyslipidemia, smoking or former smoking, chronic obstructive pulmonary disease, prior acute myocardial infarction (AMI), prior cerebrovascular accident (CVA), prior coronary angioplasty (CA), prior myocardial revascularization (CABG) and chronic renal failure requiring dialysis, body mass index (BMI), medications (proton pump inhibitors, statins and calcium channel blockers); b) interventionist: number of approached vessels, approached vessels, number of implanted stents, overall stent length and procedure duration; c) laboratory: therapeutic response to aspirin measured by optical aggregometry using arachidonic acid as agonist at a concentration of 0.5 mg/mL (Helena Platelet Aggregation System, Helena Laboratories Corp., Beaumont, TX, USA), glycemia, hematocrit, platelet count and creatinine clearance. Aspirin resistance was determined by a value ≥ 20%.

The use of omeprazole and lipophilic statins (simvastatin and atorvastatin) has been attributed to clopidogrel resistance[5,16]. In order to evaluate a different effect of these drugs, proton pump inhibitors and statins were analyzed while grouped and stratified as omeprazole and others and lipophilic and hydrophilic statins (pravastatin and rosuvastatin), respectively.

Using the rule of events per variables for binary logistic regression[17] and estimating a prevalence of clopidogrel resistance of 45%[15] so that it would be possible to include up to eight variables in the multivariate model, the sample would have to include at least 178 patients.

Continuous variables were expressed as mean and standard deviation or median and interquartile range according to the presence or absence of normal distribution evaluated by the Kolmogorov-Smirnov test. Categorical variables were expressed as percentages. In the univariate analysis, the association between clopidogrel resistance and covariates was carried out using Student's *t* test or Mann-Whitney "U" test for continuous and Chi-square test or Fisher's exact test for categorical variables. To identify independent associations with clopidogrel resistance, multivariate logistic model was built using as independent variables the ones that had an alpha error value ≤ 10% at the univariate analysis. The statistical significance was determined by an alpha error value < 5%. All statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) release 17.0.

The project was approved by the Research Ethics Committee of Hospital Universitário Clementino Fraga Filho-UFRJ, registration # 1120/11.

Results

During the analyzed period, 458 patients underwent elective angioplasty at our service. Of these, 205 (44.7%) were included in the analysis. Figure 1 summarizes the reasons for patient exclusion. The mean platelet aggregation was 37 ± 16%. Seventy-nine patients were resistant to clopidogrel (38.5% 95% CI: 31.9 - 45.2%). The mean platelet aggregation in this group was 54 ± 7% *vs*. 24.6 ± 12% in the non-resistant group (p <0.001). Chart 1 illustrates this difference. Only 3.9% of patients showed resistance to aspirin and clopidogrel.

The general characteristics of the population and univariate analysis are shown in Table 1. The value of glycemia, previous AMI and response to aspirin were associated with greater occurrence of resistance (96.5 [IQ = 88-112.3] *versus* 103 [IQ = 95-130] p <0.001, 15.1 x 26.6%, p = 0.043 and 4 [IQ = 2-6] 6 x [IQ = 4-12], p <0.001, respectively for non-resistants and resistants). There was no association between use of proton pump inhibitors (12.7 x 8.9%, p = 0.397) or lipophilic statins, atorvastatin and simvastatin (56.3 x 46.8%, p = 0.375) and clopidogrel resistance.

In the multivariate analysis, all three were independently associated with resistance to clopidogrel. Table 2 summarizes the multivariate analysis.

Discussion

We observed a high prevalence of resistance to clopidogrel (38.5%) in this population, higher than the values found in the four meta-analyzes: 33.2[9], 25[10], 26.4[11], and 21%[12].

Aradi et al.[9] analyzed the stratified prevalence through a diagnostic method and the clinical context. When selecting studies involving stable patients on chronic therapy with clopidogrel and whose platelet aggregation was measured with light transmission aggregometry (LTA) with ADP of 5 μmoles/L, considering the maximum aggregation value as defining resistance, the result is extremely similar: 37.5% (95% CI: 30.9 - 44.1%)[18,19]. The high variability in prevalence of clopidogrel resistance found in the literature may therefore be attributed to the heterogeneity of assessment methods, treatment regimens and clinical settings studied.

Glycemia, history of AMI and antiaggregant response to aspirin showed an independent association with the occurrence of clopidogrel resistance.

Diabetes and glucose control determine the predictors of clopidogrel resistance in most studies[20,21]. Within the diabetic population, some studies show that glycemic control, in most of them measured by glycosylated hemoglobin, has an even more deleterious effect on the antiplatelet therapy profile than the disease itself[22,23]. Angiolillo et al.[24] showed that in diabetic patients receiving dual antiplatelet therapy, a high value of platelet aggregation increases the risk of major cardiac events (OR = 3.96 95% CI: 1.8 - 8.7).

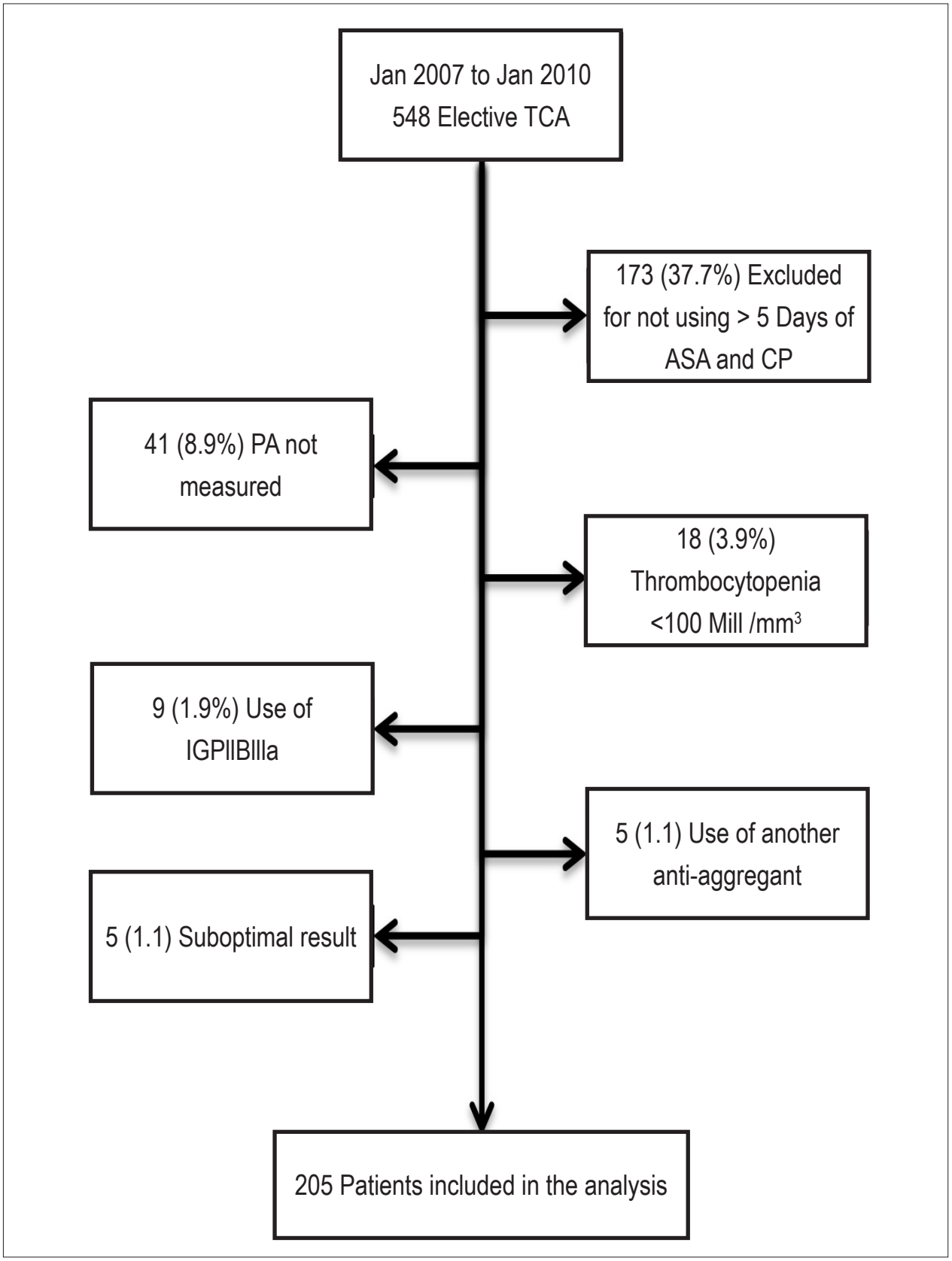

Figure 1 - *Reasons for excluding patients from the analysis; Jan: January; TCA: transluminal coronary angioplasty; PA: Platelet aggregation, CP: Clopidogrel; IGPIIbIIIa: glycoprotein inhibitors IIbIIIa.*

We, however, observed an association between the occurrence of clopidogrel resistance and blood glucose level (OR = 1.014, 95% CI: 1.004 - 1.023) and not with the presence of diabetes. The effect remains when only nondiabetic patients are included in the multivariate model (OR = 1.021 95% CI: 1.007 - 1.036).

Cardiovascular risk is related to glycemic control, regardless of diabetes diagnosis. In the study by Selvin et al.[25], each percentage point of HbA1c > 4.6% has a RR = 2.36 (95% CI: 1.43 - 3.90) in nondiabetic patients. Although there are no studies that attribute the increased risk to platelet hyperreactivity or antiplatelet resistance, this is biologically plausible.

Other authors also observed a positive correlation between resistance to clopidogrel and aspirin resistance. Gori et al.[26], using a platelet aggregation assessment method similar to that used in this study, showed a correlation coefficient of 0.536 ($p < 0.001$). Half of clopidogrel-resistant patients were also resistant to aspirin. The occurrence of dual resistance was an independent predictor of stent thrombosis and cardiac death.

Lev et al.[27], using another method for platelet aggregation assessment, showed that 47.4% of patients resistant to aspirin were also clopidogrel-resistant.

The presence of a previous history of AMI as one of the independent associations with clopidogrel resistance is a unique finding of this study. However, Gurbel et al.[8] found some data that might explain it. In their study, there was a trend toward greater use of angiotensin-converting enzyme (ACE) inhibitors in resistant patients (57 *vs*. 81%, p = 0.08). Moreover, there was a difference of 18% of patients with previous AMI in the resistant group, when compared to the non-resistant one (44 x 26%). In absolute numbers, this represents a difference greater than that found in this study (11.5%). This difference did not reach statistical significance due to the small sample size (n = 100).

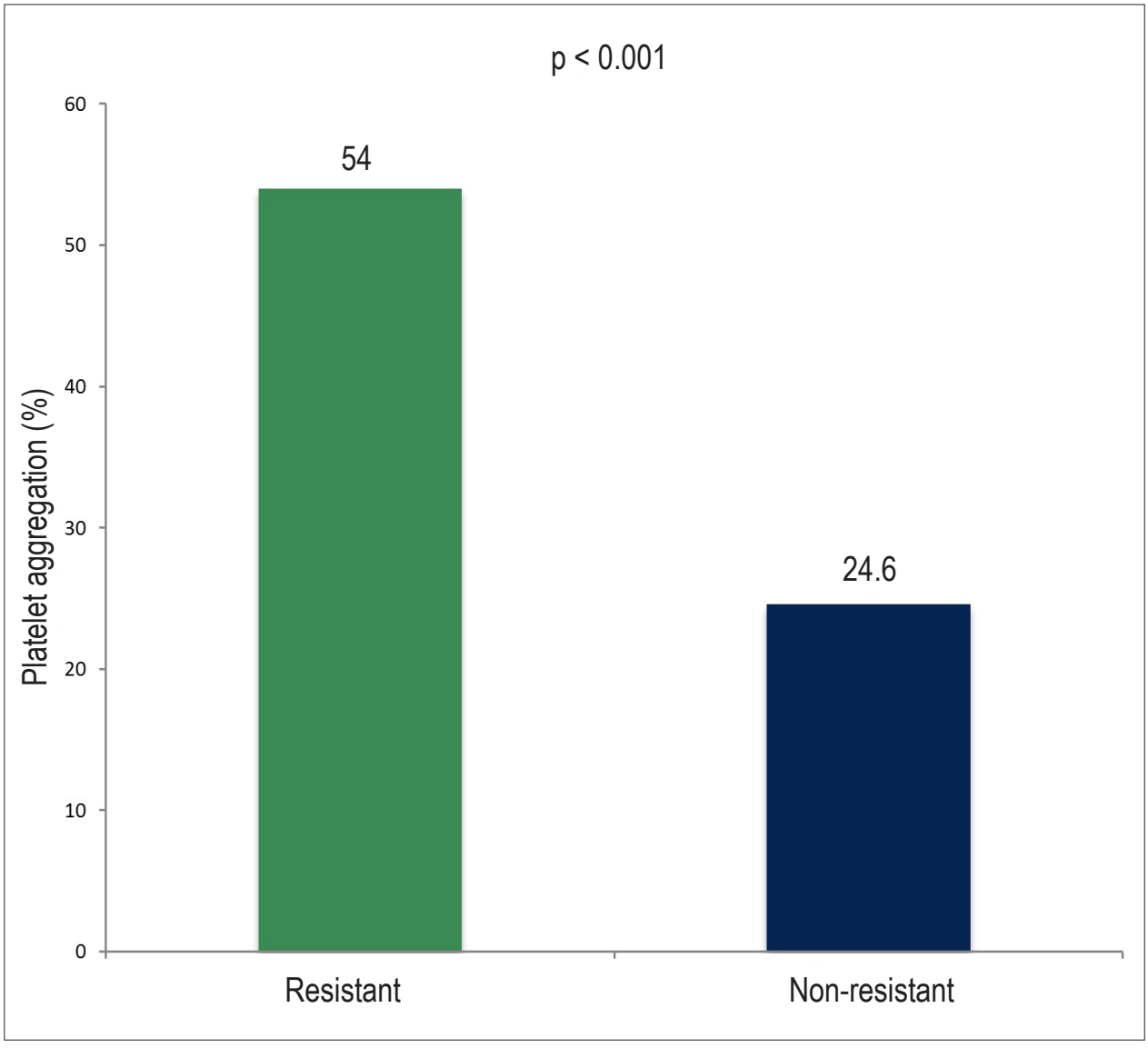

Chart 1 – *Comparison of platelet aggregation between clopidogrel resistant and non-resistant individuals*

Table 1 – Population characteristics and univariate analysis

Clinical-demographic characteristics	General	Non-Resistant (ADP < 43%)	Resistant (ADP ≥ 43%)	p value
		(N=126)	(N=79)	
Age (years)[1]	66.4 ± 11	65.6 ± 11	67.7 ± 10	0.191
Male sex (%)	61.5	62.6	59.7	0.729
Caucasian (%)	89.3	89.7	88.6	0.809
BMI(Kg/m2)	27.1 (24.7-28.4)	26.8 (24.9-28.2)	27.5 (24.6-28.4)	0.66
Creatinine Clearance (ml/min)	86.4 (70.1-96.7)	84.3 (68.3-96.4)	91.9 (71-98.8)	0.206
Glycemia(mg/dl)	98 (89-120)	96.5 (88-112.3)	103 (95-130)	< 0.001
Hematocrit (%)	37.3 (34.3-40.5)	37.6 (34.7-40.6)	37.1 (34.3-40)	0.491
Arterial hypertension (%)	71.2	68.3	75.9	0.236
Dyslipidemia(%)	71.7	71.4	72.2	0.911
Diabetes(%)	18	16.7	20.3	0.516
Smoker or ex-smoker(%)	42	40.5	44.3	0.589
COPD(%)	2.4	3.2	1.3	0.389
CABG(%)	14.1	13.5	15.2	0.734
TCA(%)	33.7	32.5	35.4	0.669
AMI (%)	19.5	15.1	26.6	0.043
CVA(%)	3.4	4.8	1.3	0.18
Medications used				
Statin (%)	67.3	70.6	62	0.201
Atorvastatin	32.2	34.1	29.1	
Simvastatin	20.5	22.2	17.7	
Pravastatin	1	0.8	1.3	
Rosuvastatin	13.7	13.5	13.9	
Statin CYP3A4+(%)	52.7	56.3	46.8	0.375
Use of PPI (%)	11.2	12.7	8.9	0.397
Omeprazole	5.4	6.3	3.8	
Pantoprazole	5.9	6.3	5.1	
Use of CCB%)	9.8	10.3	8.9	0.732
Angioplasty				
Affected vessel (%)				
LCT	3.9	4.8	2.5	0.422
Anterior descending	60	60.3	59.5	0.907
Circumflex	38.5	37.3	40.5	0.646
Right	45.9	46	45.6	0.948
Venous graft	2	1.6	2.5	0.634
Arterial graft	3.4	3.2	3.8	0.811
Total of vessels/patient(n)	1 (1-2)	1 (1-2)	1 (1-2)	0.847
Number of stents/patient(n)	2 (1-3)	2 (1-3)	2 (1-3)	0.861
Overall stent length(mm)	44 (28-64.5)	42 (30-64)	48 (28-66)	0.708
Duration of procedure (min)	50 (40-70)	50 (40-70)	50 (40-70)	0.794
Platelet Aggregation				
Platelet Measurement (103/mm3)[1]	212.2 ± 61	215.2 ± 67	207.2 ± 48	0.317
AA(%)	5 (3-8)	4 (2-6)	6 (4-12)	< 0.001
AA>20%	6.3	4	10.1	0.0708
Basal PA (%)	37 ±16	26.39 ± 10	54 ± 7	< 0.001
Final PA	28.2 ± 14	24.6 ± 12	34 ± 15	< 0.001

BMI: body mass index; COPD: Chronic obstructive pulmonary disease; CABG: coronary artery bypass surgery; TCA: transluminal coronary angioplasty; AMI: Acute myocardial infarction; CVA: cerebrovascular accident; CYP: Cytochrome P450; IBP: Proton Pump Inhibitors; CCB: calcium channel blockers; LCT: Left Coronary Trunk; AA: arachidonic acid; PA: Platelet Aggregation.

Table 2 – Multivariate Analysis

Variables	β	Standard Error	Wald	p value	OR	95%CI%
Glycemia (mg/dl)	0.014	0.005	8.086	0.004	1.014	1.004 -1.023
AMI (%)	0.843	0.380	4.918	0.027	2.323	1.103-4.892
AA (%)	0.056	0.020	7.852	0.005	1.057	1.017-1.099

AMI: acute myocardial infarction; AA: aracdonic acid

Patients with prior AMI have a higher likelihood of using ACE inhibitors. Unfortunately we cannot prove this hypothesis, as the use of ACE inhibitors was not one of the analyzed variables.

To our knowledge, this is the first national study to determine the prevalence and associations of clopidogrel resistance. A rational incorporation of new antiplatelet aggregation strategies starts with a better understanding of the clinical significance of this condition in our country.

This study has some limitations:

• Retrospective design that hinders variable control;

• Absolute majority of the patients were Caucasian, making it difficult to extrapolate these results to other ethnicities;

• PA can increase up to 7% immediately after stent implantation[28];

• PA improvement may be a temporary effect. A recent study suggests that the value 30 days after stent implantation has a better correlation with long-term events[29];

• There was no genetic evaluation of patients in order to assess other causes of resistance;

• Although it was carried out in the usual investigation format, the prior use of clopidogrel could have been assessed through an adherence questionnaire;

• We did not evaluate the use of other medications already associated with clopidogrel resistance, such as losartan and imidazole derivatives.

Conclusion

In this sample we found a high prevalence of clopidogrel resistance in patients who underwent elective angioplasty. The levels of blood glucose, history of previous AMI and response to aspirin were independently associated with this condition.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the master thesis submitted by Fabrício Braga da Silva, from UFRJ.

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