Original Article

Lack of Clopidogrel-Statin Interaction in Patients Undergoing Coronary Stent Implantation

Carlos Vicente Serrano Júnior[1], Alexandre de Matos Soeiro[1], Leila Fernandes Araújo[1], Bruna Jabot[1], Fabiana Rached[1], Noemia Mie Orii[2], José Carlos Nicolau[1], Alberto J. Duarte[2], José Antonio F. Ramires[1]

Instituto do Coração (InCor) - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo[1]; Instituto de Medicina Tropical - Faculdade de Medicina da Universidade de São Paulo[2], São Paulo, SP - Brazil

Abstract

Background: Some studies have suggested reduced activity of clopidogrel on platelet activation and adherence in patients using statins.

Objective: To assess whether platelet activation and aggregation decrease with clopidogrel, and whether there is a reduction of the action of clopidogrel when associated with atorvastatin or simvastatin.

Methods: This prospective study included 68 patients with stable angina with previous use of simvastatin, atorvastatin, or no statin (control group), with previous elective indication of percutaneous coronary intervention (PCI). Platelet activation was analyzed by means of platelet count, levels of P-selectin and glycoprotein IIb/IIIa (with and without ADP stimulation) by flow cytometry. The findings were analyzed before and after percutaneous coronary intervention and the administration of clopidogrel.

Results: We observed reduction in platelet activity with use of clopidogrel. Furthermore, no differences were found between the variables analyzed to prove reduced activity of clopidogrel when combined with statins. We observed levels of p-selectin (pre-angioplasty: 14.23 ± 7.52 x 8.83 x 11.45 ± 7.65 ± 7.09; after angioplasty: 21.49 ± 23.82 x 4 37 ± 2.71 x 4.82 ± 4.47, ρ <0.01) and glycoprotein IIb/IIIa (pre-angioplasty: 98.97 ± 0.43 ± 1.25 x 98.79 x 99.21 ± 0.40 after angioplasty: 99.37 ± 0.29 ± 1.47 x 98.50 x 98.92 ± 0.88, ρ = 0.52), respectively, in the control, atorvastatin and simvastatin groups.

Conclusion: We concluded that platelet activation decreases with administration of clopidogrel, and clopidogrel has no antiplatelet effect reduced in the presence of simvastatin or atorvastatin. (Arq Bras Cardiol 2010; 95(3): 321-327)

Key words: Hidroxymethylglutaryl-CoA reductase inhibitors; stents/utilization; simvastatin; angioplasty transluminal percutaneous coronary.

Introduction

Clopidogrel and statins are of utmost importance in the management of coronary artery diseases, contributing to reducing cardiovascular events[1-3].

The combination of clopidogrel with ASA in patients with acute coronary syndrome (ACS) without ST-segment elevation has brought great benefit, reducing the rate of cardiovascular events and mortality by 20% compared to the isolated use of ASA[4-6]. Moreover, this same drug combination in patients undergoing percutaneous coronary intervention (PCI) was also able to reduce more significantly the rates of reinfarction, mortality and urgent coronary artery bypass grafting in the

first 30 days after the PCI when compared to patients who received only ASA[4,7].

Clopidogrel has a direct and indirect action on the mechanisms of platelet activation, aggregation and adhesion. The study revealed lower incidence of thrombosis in coronary artery stent and lower rate of acute myocardial infarction, cardiovascular shock and death in patients with atherosclerotic disease using the drug[1-3]. It is an inactive thienopyridine derivative that requires hepatic metabolism by the cytochrome P450 enzyme system (CYP) 3A4[3] to perform its basic antiplatelet function by inhibiting, selectively and irreversibly, the binding of adenosine 5´-diphosphate (ADP) to the low-affinity type-2 purinergic platelet receptor[8-11]. Inhibition of platelet aggregation by clopidogrel is irreversible and concentration-dependent[12].

In turn, the main function of statins is to reduce plasma cholesterol levels (especially LDL-cholesterol), helping to slow down the progression and rupture of atherosclerotic plaque[13]. These have liver metabolism, whose basic mechanism of action consists of inhibition of 3-hydroxy-3-methylglutaryl

coenzyme A (HMG-CoA) reductase, which is the main enzyme responsible for cholesterol biosynthesis[14,15]. Both simvastatin and atorvastatin are extensively metabolized by cytochrome P-450 3A4 (CYP3A4). Simvastatin is a specific competitive inhibitor of HMG-CoA reductase, while atorvastatin stands out for causing a lasting inhibition of the enzyme[16].

Patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) are often receiving combined acetylsalicylic acid (ASA), clopidogrel and statins. However, both clopidogrel and most statins require hepatic activation through the cytochrome P-450, which may decrease the activity of clopidogrel, limiting its effectiveness and presenting a significant clinical impact[17].

Methods

This study evaluated the drug interaction between simvastatin or atorvastatin and clopidogrel, compared to a control group without statin use. The main purpose of the study was to assess whether: 1) platelet activation and aggregation decreased with administration of clopidogrel, 2) there is a reduction of clopidogrel action on platelet activation and aggregation, when combined with atorvastatin or simvastatin.

Thus, we evaluated platelet activation and aggregation of three groups of patients with stable angina undergoing PCI with conventional stenting.

This is a prospective study that included patients with stable angina with previous use of simvastatin or atorvastatin, or no statin, who had previous elective indication, according to the routines of the Hemodynamics Laboratory, of percutaneous coronary intervention. The study protocol was approved by the Ethics and Research Committee and all patients signed an informed consent before being enrolled.

All patients have been using ASA (100-200 mg/day). Immediately before the ICP, patients received 300 mg of clopidogrel followed by 75 mg/day. Patients were divided as follows: patients using atorvastatin (10-40 mg/day); patients using simvastatin (10-40 mg/day); and patients not using any type of statin (control group).

Sample size calculation

We included 83 patients, of which eight patients were included in the control group, 37 patients in the atorvastatin group and 38 in the simvastatin group. Based on an alpha error of 0.01 and using a power of 0.9 for primary outcomes, we calculated the number of individuals required for the study at approximately 25 in each group using statins, according to previous studies[4,5,7,17] that evaluated the interaction between statins and clopidogrel.

Inclusion criteria

a. Adult men and women aged between 40 and 80 who will undergo PCI with conventional stenting.

b. History of stable angina.

c. Patients who did not receive any statin (control group), or those using atorvastatin (atorvastatin group) or simvastatin

(simvastatin group) for more than 30 days.

d. Consent form signed.

Exclusion criteria

a. Pregnancy.

b. Significant valvular disease.

c. History of unstable angina or myocardial infarction at the time and in the last three months.

d. Abnormality on electrocardiogram indicating the possibility of ACS (ST-segment depression or elevation).

e. History of acute or chronic inflammatory disease.

f. History of cancers.

g. History of disease involving hypercoagulability or coagulopathy.

h. Use of drug-coated coronary stents.

i. Concomitant use of glycoprotein inhibitors (GP) IIb/IIIa.

Experimental protocol

After the selection of patients for the study, two venous blood samples were taken. We collected 10 ml of blood at admission, before administration of clopidogrel. Other 10 ml of blood were collected 24 hours after drug administration and PCI. All patients received clopidogrel at a dose of 300 mg and unfractionated heparin 5,000 IU intravenously, both upon the PCI. Punctures were made with special care not to stimulate platelet activity. With these samples, we analyzed the state of platelet activation by measuring the number of platelets and levels of P-selectin and GP IIb/IIIa (with and without ADP stimulation) by flow cytometry. The findings were analyzed before and after PCI and administration of clopidogrel.

Flow cytometry

Measurements of CD41 expression (a_{IIb} b_3 complex) and CD62P (GMP-140) in platelets were performed by flow cytometry. The CD41 is a monoclonal antibody that reacts with complexed IIb glycoprotein and IIIa glycoprotein. Immediately after collection, whole blood samples were diluted and incubated with saturating concentrations of anti-human CD41 monoclonal antibody (mAb) combined with fluorescein isothiocyanates (FITC) and anti-human CD62P mAb combined with phycoerythrin (PE). The anti-human CD41 mAb is produced from the clone P2, Immunotech (hybridoma SP2/0-Ag.14 myeloma X Balb/C spleen cells) and reacts with the subunits a_{IIb} e b_3 in an inhibiting complex of platelet aggregation induced by ADP, thrombin and collagen. The anti-human CD62P mAb is produced from the clone CLB-Thromb/6, Immunotech (hybridoma SP2/0 Ag x 1.4 x Balb/cx Aj spleen cells) and recognizes the GMP-140 expressed in activated platelets. Anti-immunoglobulins G_1 (Immunotech) were used as control and combined with FITC and PE to adjust the nonspecific binding of the antibody. To assess platelet reactivity, whole blood aliquots were incubated at room temperature for 15 min with 1 mmol/L of ADP. Incubation with antibodies was performed for 20 minutes at 4°C and the samples were analyzed by the flow cytometer Coulter Electronics. The fluorescence of fluorescein was detected using

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a 530/30 mm filter, and the phycoerythrin fluorescence was detected with a 585/42 mm filter.

Statistical analysis

The descriptive analysis of the study population includes median and standard deviation values for each clinical variable analyzed. The comparison between baseline categorical variables was performed by χ^2 test and continuous variables by Student t test.

To evaluate the patterns of the samples compared, we used the Kolmogorov-Smirnov test. The statistical analysis of the variables expressing platelets, P-selectin and GP IIb/IIIa was calculated by testing Wilcoxon signals through comparisons among the same group selected before and after the PCI. In comparisons between different groups before or after PCI, Kruskal-Wallis test was applied, and when a statistical difference was observed, we used the Dunn test to discriminate differences. For all calculations, p <0.05 values were considered statistically significant. The analysis was performed using the software SPSS V. 10.0.

A) Specific variables

Clinical variables: age, sex, risk factors for atherosclerosis (family history, hypercholesterolemia, hypertension, smoking), and use of other drugs that may interfere with the hepatic metabolism of clopidogrel (diltiazem, dexamethasone, phenytoin).

Laboratory variables: platelet count (platelets/mm³ [normal between 150,000 and 500,000 platelets/mm³], P-selectin and GP IIb/IIIa levels (with and without ADP).

B) Outcomes

Values of platelet count, P-selectin and GP IIb/IIIa levels (with and without ADP).

Limitations

Due to the small sample of patients, it was not possible to analyze the clinical outcomes, although the preliminary purpose of this study is more mechanistic than clinical analysis. In addition, we analyzed the relationship of the association of clopidogrel only with simvastatin and atorvastatin. It should not be inferred that there is no inhibiting effect of the action of clopidogrel with other statins.

Results

The clinical characteristics of the study population are shown in Table 1. One patient in the control group, four patients in the simvastatin group and three patients in the atorvastatin group were taking diltiazem, a drug that can produce drug interaction with clopidogrel. Differences were observed in previous acute myocardial infarction, dyslipidemia and hypertension, probably due to the smaller number of individuals included in the control group and because patients with other risk factors or history of atherosclerotic disease are recommended to attain tighter lipid control goals, which imposes stronger indication for use of statins in these patients.

Table 1 - Clinical characteristics of the population

	CT (n = 8)	Atorv (n = 37)	Simv (n = 38)	p
Age (years)	58 ± 11	64 ± 10	62 ± 10	0.3
Men (%)	78	56	65	0.4
Body mass index (kg/m²)	29 ± 5	29 ± 5	28 ± 5	0.3
Active smoking (%)	13	14	13	0.8
Positive family history (%)	38	53	55	0.7
Previous CVA (%)	0	14	13	0.3
Diabetes (%)	25	30	33	0.9
Previous MI (%)	13	62	51	0.03
Dyslipidemia (%)	38	92	100	< 0.001
Hypertension (%)	63	92	97	0.02

CVA - cerebrovascular accident, MI - myocardial infarction; CT - control group; Atorv - group using atorvastatin; Simv - group using simvastatin.

Table 2 shows the count of the absolute number of platelets before and after PCI. Differences were analyzed within each of the groups studied, observing a significant reduction after administration of clopidogrel.

Table 3, Figures 1 and 2, show the comparison of the results of P-selectin and GP IIb/IIIa parameters before and after PCI.

Aiming to evaluate the potential of platelet activation after blood collection and in its manipulation, platelet samples were stimulated with ADP in additional experiments. Using as an example the group of patients using atorvastatin, we describe in Table 4 the control of samples used in the study, showing that the manipulation in the collection did not activate the platelets, because the ADP induced significant changes to the variable P-selectin. Consequently, we also found that after administration of clopidogrel, in the collection taken after the PCI, there was a reduction of P-selectin values before and after ADP stimulation, compared to the results found before the PCI, without clopidogrel, which reveals that the clopidrogrel minimized the stimulatory effects of ADP on P-selectin.

Discussion

In our study, we found that patients who used both simvastatin and atorvastatin, had no antiplatelet effect changed for using clopidogrel. That is, no interference was found between these two statins and platelet inhibition.

Table 2 - Concentration of platelets (platelets/mm³ of blood) before and after percutaneous coronary intervention

	CT (n = 7)	Atorv (n = 31)	Simv (n = 30)
Pre-PCI	209.000 ± 53.435	228.451 ± 46.457	241.363 ± 70.493
Post-PCI	184.428 ± 29.211	209.774 ± 40.778	221.818 ± 68.673
p	0. 04	0. 006	0. 001

CT - control group; Atorv - group using atorvastatin; Simv - group using simvastatin.

Table 3 - **Results of the parameters P-selectin (CD62P) and glycoprotein IIb/IIIa (CD41) before and after percutaneous coronary intervention for the control groups using atorvastatin and simvastatin**

	Pre-PCI			Post-PCI		
	CT (n = 7)	Atorv (n = 31)	Simv (n = 30)	CT (n = 7)	Atorv (n = 31)	Simv (n = 30)
P-selectin	14.23 ± 7.52	11.45 ± 8.83	7.65 ± 7.09ᶦ	21.49 ± 23.82	4 .37± 2.71*	4.82 ± 4.47*
GP IIb/IIIa	98.97 ± 0.43	98.79 ± 1.25	99.21 ± 0.40	99.37 ± 0.29	98.50 ± 1.47	98.92 ± 0.88

PCI - percutaneous coronary intervention; CT - control; Atorv - atorvastatin; Sinv - simvastatin; GP - glycoprotein. *= P <0.01 vs pre-PCI, intragroup; ᶦ= ρ <0.05 vs CT, pre-PCI.
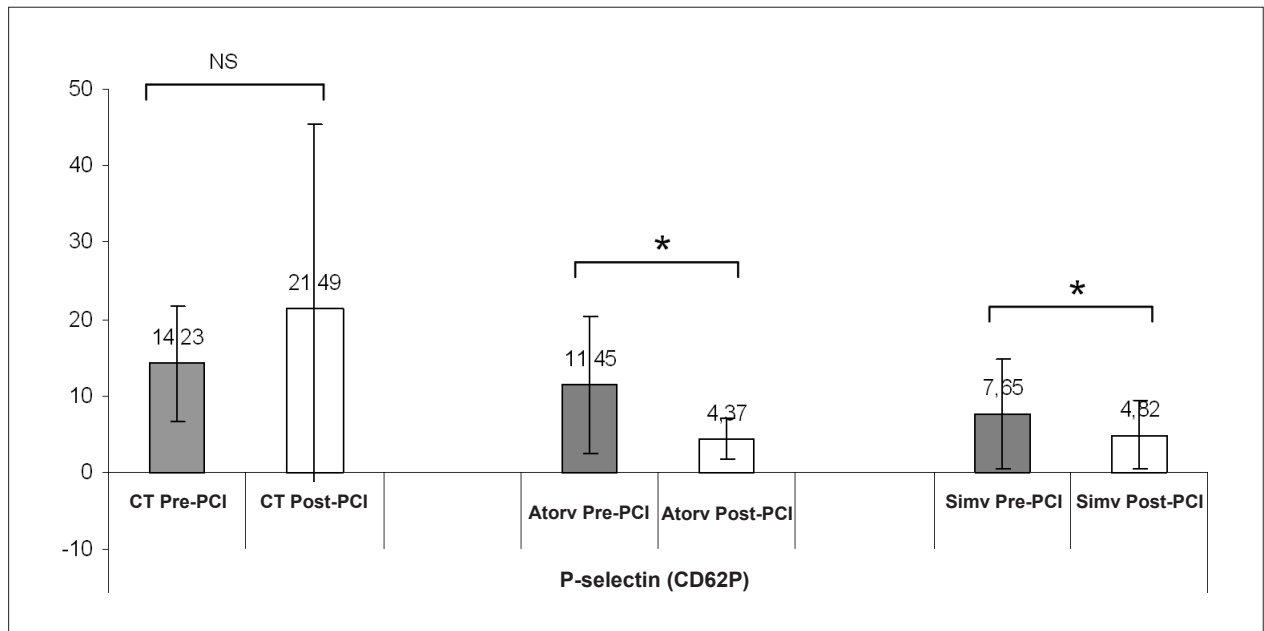

Figure 1 - *Comparison of parameters P-selectin (CD62P) before and after percutaneous coronary intervention for the control groups using atorvastatin and simvastatin. PCI - percutaneous coronary intervention; CT - control; Atorv - atorvastatin; Simv - simvastatin. *= ρ < 0.01 vs pre-PCI, intra-group; NS - not significant.*
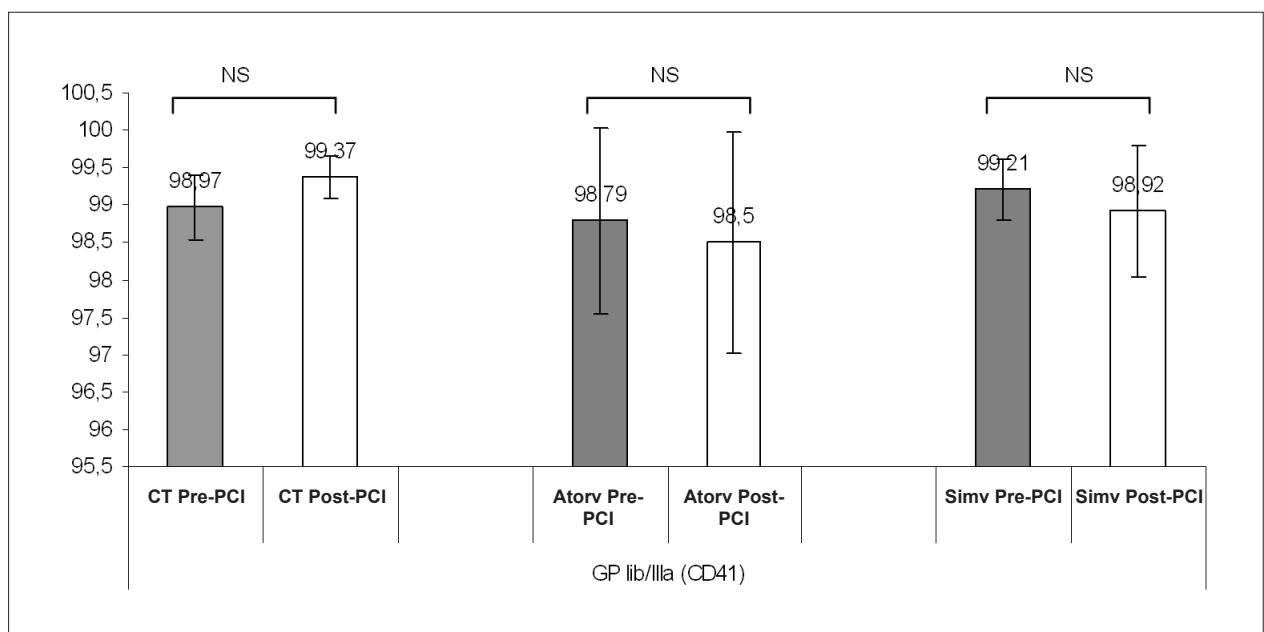

Figure 2 - *Comparison of parameters glycoprotein IIb/IIIa (CD41) before and after percutaneous coronary intervention for the control groups using atorvastatin and simvastatin. PCI - percutaneous coronary intervention; CT - control; Atorv - atorvastatin; Simv - simvastatin; GP - glycoprotein. NS - not significant.*

Table 4 - Results of platelet samples before and after ADP stimulation before and after percutaneous coronary intervention, the group of patients using atorvastatin

	Pre-PCI		Post-PCI	
	Without ADP	With ADP	Without ADP	With ADP
P-selectin (n = 31)	11.45 ± 8.83	73.10 ± 14.59	4.37 ± 2.71*	52.63 ± 19.50¡
GP IIb/IIIa (n = 31)	98.79 ± 1.25	98.93 ± 0.48	98.50 ± 1.47	98.90 ± 0.58

PCI - percutaneous coronary intervention; GP - glycoprotein. *= $p<0.001$ vs pre-PCI, intra-group (without ADP) = ¡=$p < 0.001$ vs pre-PCI, intra-group ¡with ADP).

We observed a significant reduction in the level of platelet P-selectin in simvastatin and atorvastina groups after percutaneous coronary intervention and administration of clopidogrel, which shows the effectiveness of the drug even in patients using statins. The control group showed an increase in the level of P-selectin after PCI, probably due to the small number of patients and the high standard deviation observed in the second collection of this group. Unlike other studies, our study assessed platelet function by means of two platelet markers concurrently (GP IIb/IIIa and P-selectin).

Other studies analyzed the actual existence of pharmacological interaction of clopidogrel with statins, especially those metabolized by cytochrome P450 (CYP) 3A4, such as simvastatin and atorvastatin[4,7,18-22].

Lau et al[4] analyzed patients who underwent PCI and evaluated platelet aggregation 24 hours and six to eight days after administration of clopidogrel. The study revealed a decrease in the antiplatelet action of clopidrogrel when administered with atorvastatin in a dose dependent manner, compared with pravastatin, a hydrophilic statin not metabolized by CYP3A4. One of the explanations for these results may be because the authors have measured platelet aggregation by analysis at the bedside, indirectly obtaining platelet aggregation, while other studies used aggregation techniques through optical transmission, flow cytometry or combinations of tests that measure platelet aggregation[4].

The prospective study INTERACTION (The Interaction of Atorvastatin and Clopidogrel Study) studied patients taking atorvastatin, no statin or other statins, undergoing coronary stenting[7]. These patients received a loading dose of 300 mg of clopidogrel immediately before the PCI. There were no differences in platelet inhibition 4 and 24 hours after administration of clopidrogrel, regardless of using different statins, by aggregation techniques well defined as flow cytometry and aggregation by optical transmission[7].

Trenker et al[18] performed a retrospective analysis involving the study EXCELSIOR (Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement). We evaluated patients with symptomatic coronary disease undergoing elective PCI and compared statins metabolized by CYP3A4 with a group not using statins. We analyzed the antiplatelet effects of administration of a loading dose of 600 mg of clopidogrel in these patients. There were no reductions in the antiplatelet action of clopidogrel when combined with simvastatin or atorvastatin. There were also no differences in clinical outcomes of patients after PCI[18]. Subanalyses of other studies such as PROVE-IT TIMI-22 and CHARISMA-Trial showed no differences in clinical events in patients using different types of statins (atorvastatin, pravastatin, lovastatin and simvastatin)[23,24].

We were interested in studying simvastatin and atorvastatin for being widely used in medical practice in Brazil and because both are metabolized by CYP3A4. Simvastatin is a specific competitive inhibitor of HMG-CoA reductase, while atorvastatin causes a lasting inhibition of the enzyme[16].

It is speculated that statins have pleiotropic interesting effects[25-27] in handling patients with coronary artery disease, besides reducing cholesterol levels. Two of these supposed effects still under study include: (a) an anti-inflammatory role, resulting in atherosclerotic plaque stabilization and reduced inflammatory mediators (cytokines and soluble adhesion molecules); and (2) decreased platelet activity[25-27]. Antiplatelet and antithrombotic effects concerning the use of statins have been recently reported, showing inhibition of platelet activation in patients with hypercholesterolemia after one to four weeks of treatment. However, this is still under initial studies, and it is probably associated with the link between platelets and oxidized LDL[28].

Interestingly, our findings clearly define that these statins did not affect markers of platelet activation and aggregation in the administration of clopidogrel. Specifically, there were no significant changes in the expression of GP IIb/IIIa after ADP stimulation before (without clopidrogrel) or after PCI (with clopidrogrel), suggesting that these two stimuli (chemical stimulation with APD and mechanical stimulation with PCI) do not act on the expression of platelet GPIIb/IIIa.

Our findings underscore the importance of the concomitant use of statins and clopidogrel in patients undergoing elective PCI due to the advantages that each of these drugs have in this scenario. Recently, the importance of using statins in patients undergoing PCI was well demonstrated in the study ARMIDA-ACS (Atorvastatin pretreatment improves outcomes in patients suffering from acute coronary syndromes undergoing early percutaneous coronary intervention) in which pre-treatment with high atorvastina doses leads to favorable clinical outcomes in patients with high-risk acute coronary syndrome[29].

Conclusion

Based on the results of this study, we conclude that platelet activation actually decreases with administration of clopidogrel. Besides this, we observed that clopidogrel

has no antiplatelet effect reduced in the presence of statins metabolized by cytochrome P450 (CYP) 3A4, such as simvastatin and atorvastatin.

Potential Conflict of Interest

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

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