Use of platelet glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: 10-year experience in Brazil

Uso de inibidores da glicoproteína IIb/IIIa na intervenção coronária percutânea primária: experiência de 10 anos no Brasil

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ABSTRACT – Background: Individualized use of glycoprotein IIb/IIIa inhibitors during primary percutaneous coronary intervention in scenarios with high thrombotic load or occurrence of coronary flow abnormalities may be considered, despite scarce scientific evidence. Our objective was to compare patients undergoing primary percutaneous coronary intervention treated or not with glycoprotein IIb/IIIa inhibitors during the procedure. **Methods:** A national, multicenter, retrospective study that included consecutive patients undergoing primary percutaneous coronary intervention, treated or not with glycoprotein IIb/IIIa inhibitors, between June 2006 and March 2016, using the database of the *Central Nacional de Intervenções Cardiovasculares* (CENIC). **Results:** We enrolled 18,690 patients, of which 3,032 (16.2%) received glycoprotein IIb/IIIa inhibitors. The mean age was 61.5±12.4 years, 69.5% were men, and 19.9% had diabetes mellitus. The group receiving glycoprotein IIb/IIIa inhibitors had a higher prevalence of long, thrombotic, bifurcation lesions, occlusions or TIMI flow grade <2. This group showed higher mortality (3.7% vs. 4.8%; p=0.0046), reinfarction (0.5% vs. 1.1%; p<0.0001) and major adverse cardiac event rates (4.0% vs. 5.7%; p<0.0001). In the univariate analysis, the use of glycoprotein IIb/IIIa inhibitors was associated with a higher chance of death (RR 1.31; 95%CI 1.09-1.58; p=0.0048), but was not confirmed as an independent predictor in the multivariate analysis. **Conclusion:** Among patients undergoing primary percutaneous coronary intervention, the group treated with glycoprotein IIb/IIIa inhibitors had greater clinical severity and anatomical complexity, and worse in-hospital clinical outcomes.

KEYWORDS: Acute coronary syndrome; Angioplasty; Myocardial infarction; Platelet aggregation inhibitors

RESUMO – Introdução: O uso individualizado dos inibidores da glicoproteína IIb/IIIa durante a intervenção coronária percutânea primária, em cenários com alta carga trombótica ou ocorrência de alterações de fluxo coronariano, pode ser considerado, apesar da escassez de evidências científicas. Nosso objetivo foi comparar pacientes submetidos à intervenção coronária percutânea primária que receberam ou não inibidores da glicoproteína IIb/IIIa durante o procedimento. **Métodos:** Estudo multicêntrico nacional, retrospectivo, que incluiu pacientes consecutivos submetidos à intervenção coronária percutânea primária, tratados ou não com inibidores da glicoproteína IIb/IIIa, no período de junho de 2006 a março 2016, sendo utilizado o banco de dados da Central Nacional de Intervenções Cardiovasculares (CENIC). **Resultados:** Foram incluídos 18.690 pacientes, dos quais 3.032 (16,2%) receberam inibidores da glicoproteína IIb/IIIa. A média de idade foi de 61,5±12,4 anos, sendo 69,5% do sexo masculino e 19,9% portadores de diabetes melito. No grupo que recebeu inibidores da glicoproteína IIb/IIIa, constatou-se maior prevalência de lesões longas, trombóticas, envolvendo bifurcações, oclusões ou fluxo TIMI <2. Esse grupo mostrou maior mortalidade (3,7% vs. 4,8%; p=0,0046), reinfarto (0,5% vs. 1,1%; p<0,0001) e eventos cardíacos adversos maiores (4,0% vs. 5,7%; p<0,0001). Na análise univariada, o uso de inibidores da glicoproteína IIb/IIIa associou-se a maior chance de óbito (RC 1,31; IC95%: 1,09-1,58; p=0,0048), mas não se confirmou como preditor

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independente na análise multivariada. **Conclusão:** Entre pacientes submetidos à intervenção coronária percutânea primária, o uso de inibidores da glicoproteína IIb/IIIa caracteriza um grupo de maior gravidade clínica, complexidade anatômica e pior evolução hospitalar.

Palavras-chave: Síndrome coronariana aguda; Angioplastia; Infarto do miocárdio; Inibidores da agregação de plaquetas

INTRODUCTION

Adjunctive platelet glycoprotein (GP) IIb/IIIa inhibitors in acute coronary syndrome (ACS) aims to reduce thrombus load and restore coronary perfusion. Despite appropriate reestablishment of coronary flow after primary percutaneous coronary intervention (PCI), distal embolization of atherothrombotic debris may negatively impact the microcirculation, which represents a relevant application of these drugs with high antiplatelet action.¹⁻⁴

Before the advent of the dual antiplatelet therapy currently in use, studies like EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade) and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial) showed a combined reduction in major adverse cardiac events (MACE) and boosted the use of GP IIb/IIIa inhibitors in ACS.⁵⁻⁸ In Brazil, only tirofiban and abciximab are commercially available.⁹

In combination with current antithrombotic therapies, routine use of GP IIb/IIIa inhibitors is not beneficial, and can lead to higher rates of severe bleeding.¹⁰ Individualized use may be considered in specific situations, such as high thrombotic load, slow/no reflow phenomenon, coronary dissections, or other thrombotic complications.^{11,12}

This study aimed to compare the profile and in-hospital outcomes of patients subjected to primary PCI, treated or not with adjunctive GP IIb/IIIa inhibitors, in addition to verifying the influence of variables of interest on mortality.

METHODS

A national, multicenter, retrospective study of all consecutive patients subjected to primary PCI, between June 2006 and March 2016, comparing patients treated or not with GP IIb/IIIa inhibitors during the procedure. Data were collected from the database of the *Central Nacional de Intervenções Cardiovasculares* (CENIC; <http://www.corehemo.net/>).

Patients were characterized by clinical, angiographic, procedure-related and MACE criteria during the hospital phase, including the occurrence of death, non-fatal infarction or urgent coronary artery bypass surgery (CABG). This study follows the recommendations of the Declaration of Helsinki and Resolution 466/12 of the National Health Council and has been approved by the local ethics committee under protocol 2.992.506 (CAAE: 01989218.2.0000.5485).

Statistical analysis

Descriptive statistics were presented for clinical, angiographic and procedure-related characteristics, in-hospital clinical outcomes, and procedural success in patients eligible for the analysis. For continuous variables, mean and standard deviation was presented and, for categorical variables, contingency tables were presented with absolute and percentage frequencies.

Comparative analysis of categorical variables was performed using the Chi-square test and, when necessary, the likelihood ratio. Continuous variables were compared using the Student's *t* test. For multiple comparisons, we used the Bonferroni correction.

To assess the influence of variables of interest on mortality, the simple logistic regression model was used. The independent variables in the univariate regression model were tested with the forward selection method and included in the multivariate analysis. Variables with high loss of information (e.g. ventricular dysfunction and collateral circulation) were disregarded in the multiple analysis. For all analyses, the level of significance was set as $p < 0.05$.

RESULTS

A total of 18,690 patients were analyzed, with mean age of 61.5 ± 12.4 years, of which 69.5% were men, and 19.9% had diabetes mellitus. The clinical characteristics are listed in Table 1, and Killip class 1 was the most prevalent (76.6%). When comparing the groups, patients who received GP IIb/IIIa inhibitors had a lower mean age (60.7 years vs. 61.6 years; $p = 0.0001$) and a higher prevalence of males (71.6% vs. 69.1%; $p = 0.0058$), smoking (38.3% vs. 33.1%; $p < 0.0001$) and diabetes mellitus (22.7% vs. 19.3%; $p < 0.0001$). The prevalence of hypertension (73.1% vs. 69.1%; $p < 0.0001$), prior PCI (12.3% vs. 9.3%; $p < 0.0001$) and Killip class 1 (77.6% vs. 71.4%; $p < 0.0001$) was higher in the group not treated with GP IIb/IIIa inhibitors.

Patients treated with GP IIb/IIIa inhibitor infusions had greater anatomical complexity (Table 2). There was a higher prevalence of types B₂/C lesions (88.8% vs. 86.7%; $p = 0.02$), thrombotic lesions (69.8% vs. 53.2%; $p < 0.0001$), long lesions (39.3% vs. 29.6%; $p < 0.0001$), bifurcation lesions (27.1% vs. 24.3%; $p = 0.0003$), occlusions (71.7% vs. 65.6%; $p < 0.0001$), two-vessel (30.2% vs. 29.9%; $p = 0.02$) or three-vessel coronary artery disease (23.7% vs. 22.0%; $p = 0.02$). For the procedure-related characteristics listed in Table 3, there was no difference in the success rate between the groups (92.9% vs. 92.9%; $p = 0.92$), as well as in final Thrombolysis in Myocardium Infarction (TIMI)-flow grades 2 or 3 (97.0% vs. 96.5%; $p < 0.161$).

Regarding in-hospital clinical outcomes, mortality was higher (4.8% vs. 3.7%; $p = 0.0046$) in the group treated with GP IIb/IIIa inhibitors, as well as the incidence of MACE (5.7% vs. 4.0%; $p < 0.0001$) and reinfarction (1.1% vs. 0.5%; $p < 0.0001$) (Table 4). In the univariate analysis,

Table 1. Clinical characteristics

Characteristics	Glycoprotein IIb/IIIa inhibitors		Total (n=18,690 patients)	p-value
	No (n=15,658 patients)	Yes (n=3,032 patients)		
Age, years	61.6±12.5	60.7±12.1	61.5±12.4	0.0001
Male sex	10,822 (69.1)	2,172 (71.6)	12,994 (69.5)	0.005
Smoking	5,178 (33.1)	1,160 (38.3)	6,338 (33.9)	<0.0001
Hypertension	11,380 (73.1)	2,095 (69.1)	13,475 (72.4)	<0.0001
Dyslipidemia	7,517 (48.5)	1,505 (49.7)	9,022 (48.7)	0.240
Diabetes mellitus	2,879 (19.3)	681 (22.7)	3,560 (19.9)	<0.0001
Prior acute MI	1,479 (9.9)	275 (9.2)	1,754 (9.8)	0.223
Prior PCI	1,867 (12.3)	269 (9.3)	2,136 (11.8)	<0.0001
Prior CABG	418 (2.7)	78 (2.6)	496 (2.7)	0.730
Killip				<0.0001
1	12,143 (77.6)	2,164 (71.4)	14,307 (76.6)	
2	2,003 (12.8)	504 (16.6)	2,507 (13.4)	
3	593 (3.8)	112 (3.7)	705 (3.8)	
4	910 (5.8)	252 (8.3)	1,162 (6.2)	

Results expressed as mean ± standard deviation or n (%). MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery.

Table 2. Angiographic characteristics

Characteristics	Glycoprotein IIb/IIIa inhibitors		Total (n=18,963 procedures)	p-value
	No (n=15,882 procedures)	Yes (n=3,081 procedures)		
Extension of the coronary disease				0.024
Single vessel	7,440 (47.8)	1,386 (45.6)	8,826 (47.5)	
Two-vessel	4,647 (29.9)	917 (30.2)	5,564 (29.9)	
Three-vessel	3,425 (22.0)	720 (23.7)	4,145 (22.3)	
LMCA	45 (0.3)	17 (0.6)	62 (0.3)	
Multi-vessel + LMCA	2 (0.01)	1 (0.03)	3 (0.01)	
Treated vessels				<0.0001
RCA	6,795 (36.5)	1,496 (40.2)	8,291 (37.1)	
LCx	2,672 (14.3)	456 (12.3)	3,128 (14.0)	
LAD	8,758 (47.0)	1,670 (44.9)	10,428 (46.7)	
Venous graft	222 (1.2)	60 (1.6)	282 (1.3)	
LMCA	179 (1.0)	40 (1.1)	219 (1.0)	
Type B ₂ /C lesions	4,858 (86.7)	1,464 (88.8)	6,322 (87.2)	0.025
Calcified lesions	3,685 (19.8)	782 (21.0)	4,467 (20.0)	0.088
Thrombotic lesions	9,916 (53.2)	2,598 (69.8)	12,514 (56.0)	<0.0001
Lesions >20 mm	5,512 (29.6)	1,464 (39.3)	6,976 (31.2)	<0.0001
Bifurcation lesions	4,535 (24.3)	1,010 (27.1)	5,545 (24.8)	0.0003
Occlusions	12,168 (65.6)	2,669 (71.7)	14,837 (66.6)	<0.0001
TIMI flow pre				<0.0001
0/1	12,631 (67.8)	2,813 (75.6)	15,444 (69.1)	
2/3	5,993 (32.2)	909 (24.4)	6,902 (30.9)	
Left ventricular dysfunction	7,588 (81.5)	1,540 (88.9)	9,128 (82.7)	<0.0001
Collateral circulation	2,453 (20.6)	734 (29.4)	3,187 (22.1)	<0.0001

Results expressed as n (%). LMCA: left main coronary artery; RCA: right coronary artery; LCx: left circumflex artery; LAD: left anterior descending artery; TIMI: Thrombolysis in Myocardial Infarction.

the use of GP IIb/IIIa inhibitors was associated with a greater chance of death (RR 1.31; 95%CI: 1.09-1.58; $p=0.0048$), but it was not confirmed as an independent predictor in the multivariate analysis. In the latter, the variables that

best correlated with mortality were age, female gender, hypertension, dyslipidemia, diabetes mellitus, prior infarction, Killip class, and extent of the coronary artery disease (Table 5).

Table 3. Procedure characteristics

Characteristics	Glycoprotein IIb/IIIa inhibitors		Total (n=18,963 procedures/ n=22,027 stents)	p-value
	No (n=15,882 procedures/ n=18,115 stents)	Yes (n=3,081 procedures/ n=3,912 stents)		
Treated vessels/patient	1.2±0.5	1.2±0.5	1.2±0.5	0.999
Use of stent	14,382 (91.7)	2,943 (97.7)	17,325 (92.7)	<0.0001
Stent/patient ratio	1.3±0.5	1.3±0.6	1.3±0.5	<0.0001
Drug-eluting stents	1,196 (6.6)	245 (6.3)	1,441 (6.5)	0.228
Stent diameter, mm	3.07±0.47	3.17±0.48	3.09±0.47	<0.0001
Stent length, mm	20.4±6.7	21.2±6.5	20.5±6.7	<0.0001
Thromboaspiration	611 (3.4)	487 (12.4)	1,098 (5.0)	<0.0001
TIMI flow post				0.161
0/1	552 (3.0)	136 (3.5)	688 (3.1)	
2/3	17,551 (97.0)	3,773 (96.5)	21,324 (96.9)	
Stenosis grade				
Pre	96.2±8.5	97.2±7.4	96.4±8.4	<0.0001
Post	4.3±10.7	3.1±9.9	4.1±10.6	<0.0001
Procedural success	14,756 (92.9)	2,861 (92.9)	17,617 (92.9)	0.920

Results expressed as mean ± standard deviation and n (%). TIMI: Thrombolysis in Myocardium Infarction.

Table 4. In-hospital clinical outcomes

Outcome	Glycoprotein IIb/IIIa inhibitors		Total (n=18,690 patients)	p-value
	No (n=15,658 patients)	Yes (n=3,032 patients)		
Reinfarction	68 (0.5)	32 (1.1)	100 (0.6)	<0.0001
Urgent CABG	18 (0.2)	0 (0.0)	18 (0.2)	0.162
Death	564 (3.7)	145 (4.8)	709 (3.9)	0.0046
MACE	627 (4.0)	172 (5.7)	799 (4.3)	<0.0001

Results expressed as n (%). CABG: coronary artery bypass surgery; MACE: major adverse cardiac events.

Table 5. Multiple logistic regression

Variables	Estimate	p-value	RR	95%CI
Age, years	0.03	<0.0001	1.03	1.02-1.04
Sex, female vs. male	0.28	0.0031	1.32	1.10-1.59
HTN, yes vs. no	0.28	0.0106	1.32	1.07-1.64
Dyslipidemia, yes vs. no	0.31	0.0016	1.36	1.12-1.65
Diabetes mellitus, yes vs. no	0.22	0.0329	1.25	1.02-1.54
Prior MI, yes vs. no	0.37	0.0041	1.44	1.12-1.85
Killip, I vs. IV	-3.39	<0.0001	0.03	0.03-0.04
Killip, II vs. IV	-2.34	<0.0001	0.10	0.07-0.13
Killip, III vs. IV	-1.30	<0.0001	0.27	0.20-0.37
Two-vessel vs. single-vessel	0.59	<0.0001	1.80	1.43-2.27
Three-vessel vs. single-vessel	0.84	<0.0001	2.31	1.84-2.9
LMCA vs. single-vessel	2.02	<0.0001	7.57	3.27-17.51

RR: relative risk; 95%CI: confidence interval; HTN: hypertension; MI: myocardial infarction; LMCA: left main coronary artery.

DISCUSSION

This study analyzed 18,690 patients subjected to primary PCI, of which 3,032 (16.2%) received GP IIb/IIIa inhibitors as adjunct therapy, amounting to a sizeable national case series. This group had greater clinical severity and anatomical complexity, and worse in-hospital outcomes.

Routine use of GP IIb/IIIa inhibitors did not show any benefits as an add-on therapy to PCI.^{10,12} However, in non-ST-segment elevation ACS, a meta-analysis demonstrated a discrete reduction in 30-day mortality and acute myocardial infarction rates in patients categorized as high risk (positive for myocardial necrosis markers, high thrombus load or complex lesions).¹¹ In addition, a meta-regression analysis showed that the use of GP IIb/IIIa inhibitors led to an isolated reduction of 30-day mortality rates in patients aged over 65 years, hemodynamically unstable, with diabetes mellitus or prior acute myocardial infarction.¹²

When compared to intracoronary and intravenous administration of GP IIb/IIIa inhibitors, the meta-analysis showed a significant reduction in 30-day mortality and target-vessel revascularization rates, at the expense of higher rates of severe bleeding, favoring the former;¹³ however, this finding was not further confirmed by randomized clinical trials.¹⁴ The meta-analysis by Elbadawi et al., in turn, showed a higher rate of final TIMI flow grade 3, myocardial blush grade II or III, and resolution of the ST-segment elevation, favoring the intracoronary administration without, however, any decrease in mortality, reinfarction or severe bleeding rates when compared with intravenous infusion.¹⁵ In our study, we were not able to perform any similar investigation due to missing information on the electronic data collection form.

In the more recent era of dual antiplatelet therapy with acetylsalicylic acid and P₂Y₁₂ receptor blockers, as well as the relatively frequent concomitant use of oral anticoagulants, the incidence of hemorrhagic complications in acute scenarios is not negligible. Therefore, when considering the use of GP IIb/IIIa inhibitors, one must pay attention to the increased incidence of bleeding and its prognostic impact on morbidity and mortality.⁹ Following an ACS, the efficacy, rapid onset of action, reversibility, influence of renal function, genetic variability and cost must be factored in when trying to predict the benefits of administering GP IIb/IIIa inhibitors, considering the risk of ischemia vs. hemorrhage on an individual basis.¹⁶

The limitations of this study were its retrospective nature, incomplete information on data collection forms, the non-adjudication of events, and a follow-up restricted to the hospital phase. The CENIC database is voluntarily fed by members of the *Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista* (SBHCI) and subject to subnotifications and, therefore, may not be representative of the national reality, but rather a reflection of the practice in centers that regularly contribute to the system.

CONCLUSION

Among patients with acute myocardial infarction subjected to primary percutaneous coronary intervention, the group treated with glycoprotein IIb/IIIa inhibitors had greater clinical severity, anatomical complexity, and worse in-hospital outcomes.

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Conflicts of interest

The authors have no conflicts of interest.

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