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Effects of statin pretreatment on adverse cardiac events following elective percutaneous coronary intervention

Efeito do uso de estatinas em eventos cardíacos adversos após intervenção coronária percutânea eletiva

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ABSTRACT – **Background:** Identification of risk factors for complications following percutaneous coronary intervention may contribute to appropriate management and reduction of adverse outcomes. The prior use of statins has been associated with lower prevalence of procedure-related myocardial infarction. This study set out to determine the prevalence of periprocedural myocardial infarction in elective coronary interventions, and to identify associated risk factors, with special emphasis on statin pretreatment. **Methods:** The sample comprised 249 patients submitted to elective therapeutic percutaneous coronary intervention at a referral interventional cardiology center between 2016 and 2018. Periprocedural myocardial infarction was defined according to Fourth Universal Definition of Myocardial Infarction criteria. **Results:** Periprocedural myocardial infarction and injury occurred in 26 (10.4%) and 141 (56.6%) patients, respectively. Male sex was associated with increased event rates (74.2% *versus* 57.3%; p=0.009). Statin pretreatment was correlated with lower event rates (59.8% *versus* 74.4%; 95%CI 0.29-0.92; p=0.025). Protective effects of statins remained significant following multivariate analysis accounting for sex and beta-blocker use (OR: 0.37; 95%CI 0.19-0.75; p=0.005). **Conclusion:** Periprocedural myocardial infarction and injury are common outcomes following elective percutaneous coronary intervention. Prevalence of such events was lower in patients using statins and higher in male patients. Findings of this study support positive evidence regarding the role of statins in cardiovascular protection.

Keywords: Angioplasty; Myocardial infarction; Percutaneous coronary intervention/adverse effects; Risk factors

RESUMO – **Introdução:** Reconhecer os fatores de risco para ocorrência de complicações após intervenção coronária percutânea pode contribuir para seu manejo adequado e a redução de desfechos adversos. O uso prévio de estatinas tem sido associado à menor prevalência de infarto do miocárdio relacionado ao procedimento. O estudo objetiva determinar a prevalência de infarto periprocedimento em intervenções coronárias eletivas e identificar fatores de risco associados a essa complicação, com particular interesse pelo efeito do uso prévio de estatinas. **Métodos:** Entre 2016 a 2018, foram incluídos 249 pacientes submetidos a procedimentos coronários percutâneos terapêuticos eletivos em um serviço de referência em cardiologia intervencionista. O critério de infarto do miocárdio periprocedimento seguiu a Quarta Definição Universal de Infarto do Miocárdio. **Resultados:** Infarto periprocedimento ocorreu em 26 (10,4%) pacientes e injúria miocárdica em 141 (56,6%). O sexo masculino foi associado à maior ocorrência do evento (74,2% *versus* 57,3%; p=0,009). Uso prévio de estatina correlacionou-se à menor ocorrência dos eventos (59,8% *versus* 74,4%; IC95% 0,29-0,92; p=0,025). Na análise multivariada, controlando-se as variáveis sexo e uso de betabloqueador, o efeito protetor das estatinas manteve-se significante (RC: 0,37; IC95% 0,19-0,75; p=0,005). **Conclusão:** O infarto periprocedimento e a injúria miocárdica são desfechos comuns após intervenção coronária percutânea eletiva. A prevalência desses eventos foi menor em pacientes que faziam uso de estatinas. Sexo masculino esteve relacionado à maior ocorrência desses episódios. Os resultados reforçam o corpo de evidências positivo acerca do papel das estatinas na proteção cardiovascular.

Descritores: Angioplastia; Infarto do miocárdio; Intervenção coronária percutânea/efeitos adversos; Fatores de risco

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INTRODUCTION

Since the advent of percutaneous coronary intervention (PCI),[1] the procedure has been increasingly performed over the years. Technical and pharmacological advancements led to lower unfavorable outcome rates. Still, the procedure is not free of complications, such as periprocedural myocardial infarction (MI).[2,3] According to the Fourth Universal Definition of Myocardial Infarction, PCI-related MI is confirmed by cardiac troponin elevation to values five-fold the upper reference limit in the 99th percentile within 48 hours of procedure completion, combined with clinical, electrocardiographic or imaging changes.[4]

Approximately one third of elective PCI are associated with a certain degree of myocardial injury.[5] In the United States, evidence of periprocedural MI are found in 5% to 30% of patients out of approximately 1.5 million PCI performed per year, depending on diagnostic criteria.[6] The prevalence and magnitude of myocardial injury after the procedure also vary according to disease presentation, angiographic features, adjuvant pharmacotherapy and biomarker used to detect myocardial injury.[2] The SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization) randomized clinical trial tested the impact of pretreatment with atorvastatin 80mg in more than 4,000 patients submitted to PCI, and reported a mean rate of periprocedural MI of 7.6%.[7]

Different factors are associated with periprocedural MI. These can be classified as related to patient, atherosclerotic plaque or procedure,[2,7-9] and are determinant factors of complications, which are primarily caused by distal embolization, side branch occlusion, coronary dissection, or collateral flow interruption.[8] Still, injury is more commonly diagnosed in apparently non-complicated PCI, due to atheromatous embolization in microcirculation.[2] The role of periprocedural MI in patient mortality is controversial, since conclusive evidence confirming myocardial injury as the primary cause is lacking.[5] However, this association must be accounted for, given the potential negative impact on patient prognosis.[10]

Studies have shown that periprocedural MI and myocardial injury can be reduced by appropriate pharmacological regimens.[11] Different strategies have been proposed and tested, such as the use of statins.[7] Experimental and clinical data suggest that, along with lipid-lowering properties, statins also have pleiotropic effects leading to lower rates of cardiac adverse events following PCI, through plaque stabilization and embolic event reduction.[12-14]

This study was designed to determine the prevalence of periprocedural MI in elective PCI and to analyze the role of some patient-related variables as risk factors for or protective factors against this outcome, with particular emphasis on the effects of statin pretreatment.

METHODS

An observational cross-sectional study. Data were collected through a questionnaire administered to patients undergoing elective PCI at a hospital located in the city of Curitiba (PR), between June 2016 and January 2018. Patients with stable coronary syndrome (stable angina or silent ischemia) admitted for PCI were included, and those with a diagnosis of acute coronary syndrome with or without ST segment elevation were excluded. Detectable pre-intervention troponin values were not an isolated exclusion factor.

The study included a questionnaire interrogating demographic data (age and sex) and clinical features (continuous drug use, comorbidities, prior myocardial revascularization procedures and known coronary artery or cerebrovascular disease). The questionnaire was administered by researchers prior to PCI.

Data, such as pre- and post-procedure troponin values, number of compromised vessels, electrocardiographic findings and clinical progression of patients from admission to hospital discharge, were extracted from electronic medical records following PCI. The upper limit of the reference range for normal troponin adopted in this study was 0.012μg/L (99th percentile of a healthy reference population). Hence, cardiac troponin values equal to or higher than 0.06μg/L within 48 hours of intervention, combined with clinical, electrocardiographic or imaging evidence, were defined as periprocedural MI in this sample, whereas myocardial injury was defined as isolated troponin elevation.

Data were analyzed using IBM Statistical Package for Social Science (SPSS), version 20.0. Categorical variables were compared using the Fisher's exact test. For each variable, the null hypothesis stated that the distributions of each diagnostic classification (MI and/or myocardial injury and lack of injury) were equal, whereas the alternative hypothesis stated distributions differed. As regards age, the null hypothesis stated that means did not differ between patients presenting with adverse events or not, whereas the alternative hypothesis stated means differed. P-values <0.05 were significant.

Logistic regression models adjusted for statin and each of the remaining variables (Crude models) were used to tease out the effects of statin treatment on the probability of adverse events. The null hypothesis stated that, in the presence of another variable, the probability of adverse events was equal for patients receiving statins or not, whereas the alternative hypothesis stated the probability differed. The Wald test was used to assess statistical significance ($p<0.05$). Odds ratios and respective 95% confidence intervals (CI) were estimated.

This study was approved by the Research Ethics Committee of the *Pontifícia Universidade Católica do Paraná*, opinion no. 1.541.196, CAAE 55157916.4.0000.0020.

RESULTS

The sample comprised 249 patients submitted to elective PCI. Mean patient age was 64.7 years (35 to 88 years).

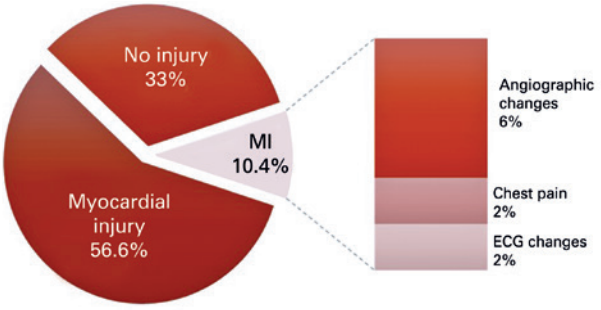
Of selected patients, 171 (68.7%) were males, 111 (44.6%) suffered from diabetes mellitus, 196 (78.7%) from arterial hypertension, and 147 (59%) from dyslipidemia. Overall, 122 (49%) patients had been submitted to coronary artery bypass graft, and 159 (63,9%) had been diagnosed as coronary artery disease. Baseline characteristics of the sample are shown in table 1.

Table 1. Baseline characteristics of the sample and distribution according to outcome

Cardiovascular risk factors	Total (n=249)	MI or injury (n=167)	No injury (n=82)	p-value
Age, years	64.7	64.9	64.3	0.6
Male sex	171 (68.7)	124 (74.2)	47 (57.3)	0.009*
Dyslipidemia	147 (59.0)	97 (58.0)	50 (61.0)	0.6
Hypertension	196 (78.7)	131 (78.4)	65 (79.3)	1.0
Diabetes mellitus	111 (44.6)	73 (43.7)	38 (46.3)	0.7
Kidney disease	13 (5.2)	10 (5.9)	3 (3.7)	0.5
Past history				
Prior percutaneous coronary intervention	122 (49.0)	84 (50.2)	38 (46.3)	0.5
Coronary artery disease	159 (63.9)	110 (52.8)	49 (59.8)	0.4
Continuous use drugs				
Statin	161 (64.7)	100 (59.8)	61 (74.4)	0.025*
ACEi/ARB	85 (34.1)	60 (35.9)	25 (30.5)	0.4
Aspirin	171 (68.7)	117 (70.0)	54 (65.8)	0.5
Beta-blocker	140 (56.2)	98 (58.6)	42 (51.2)	0.2

Results expressed as means or n (%).
The Fischer test was used for categorical variable analysis and the Student *t* test for the variable age.
*p-values <0.05 were statistically significant.
MI: myocardial infarction; ACEi: angiotensine converting enzyme inhibitor; ARB: angiotensine receptor block.

Periprocedural MI and myocardial injury occurred in 26 (10.4%) and 141 (56.6%) patients respectively (Figure 1). Of patients presenting with post-procedural events, 167 (67.1%) had MI or injury. No events were recorded in 82 (32.9%) patients.



ECG: electrocardiogram; MI: myocardial infarction.
Figure 1. Incidence of cardiovascular events following percutaneous coronary intervention.

Of patients with a confirmed diagnosis of periprocedural MI, 5 had elevated troponin values and typical symptoms lasting longer than 20 minutes, 15 had angiographic complications (7 coronary dissections, 6 abrupt occlusions of vessels and 2 angiographic thrombi), 5 had electrocardiographic changes (new left bundle branch block, ST-segment elevation) and 1 progressed to death.

Of patients presenting with events, 124 (74.2%) were male, 131 (78.4%) were hypertensive, 73 (43.7%) were diabetic, 97 (58.0%) were dyslipidemic, 10 (5.9%) had chronic kidney disease and 47 (28.1%) had undergone multivessel PCI. Male sex was associated with higher incidence of MI or myocardial injury (p=0.009). Remaining variables were not associated with increased risk of or protection against the event.

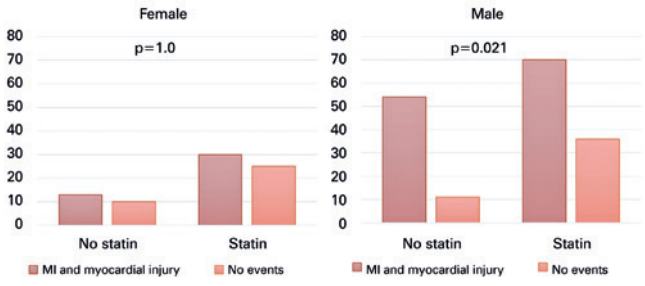
Statin use was not reported by 67 (40.1%) patients presenting with adverse events, whereas 61 (36.5%) of those free from events did report treatment with the drug. Statin use was a protective factor against the outcome (59.8% *versus* 74.4%; 95%CI 0.29-0.92; p=0.025). Logistic regression models adjusted for statin and each of the variables (crude model) revealed independent associations between statin use and lower rates of MI and myocardial injury (Table 2).

Table 2. Statin use and probability of events in the presence of remaining variables

Variable		Cases with event	Crude model	
			p-value for variable*	p-value for statin*
Age, years	Without event	64.3±9.1	0.662	0.026
	With event	64.9±10.6		
Sex			0.012	0.040
Female		55.1		
Male		72.5		
DM			0.508	0.022
No		68.1		
Yes		65.8		
HTN			0.961	0.026
No		67.9		
Yes		66.8		
CKD			0.504	0.028
No		66.5		
Yes		76.9		
Prior CAD			0.166	0.015
No		63.3		
Yes		69.2		
Prior PCI			0.452	0.023
No		65.4		
Yes		68.9		
Beta blocker			0.015	0.002
No		63.3		
Yes		70.0		
Multivessel PCI			0.440	0.027
No		65.6		
Yes		71.2		

Results expressed as mean±standard deviation or %.
p-values <0.05 are significant; Wald test.
*p<0.05.
DM: diabetes mellitus; HTN: hypertension; CKD: chronic kidney disease; CAD: coronary artery disease; PCI: percutaneous coronary intervention.

In regression analysis, male sex was an independent factor for higher event rates. Analysis of statin effects within the male patient group confirmed the association between use of this drug and lower event rates (p=0.021) (Figure 2). As regards prior use of beta-blockers, higher chances of adverse events were observed in patients on beta-blockers and not using statins. Therefore, statins had no statistically significant protective effects (p=0.216) among patients using beta-blockers but retained protective effects against MI and myocardial injury among those not using beta-blockers (p=0.004).



MI: myocardial infarction.
Figure 2. Associations between statin use and myocardial infarction and injury in male and female patients.

Protective effects of statins remained significant following model adjustment for multivariate analysis accounting for sex, statins and beta-blockers (OR: 0.37; 95%CI 0.19-0.75; p=0.005), regardless of remaining variables, as shown in table 3. Adverse event probability according to these variables were also estimated (Table 4).

Table 3. Multivariate analysis

Variable	p-value*	OR	95%CI
Sex	0.023	1.94	1.09-3.44
Beta-blocker	0.029	2.03	1.07-3.83
Statin	0.005	0.37	0.19-0.75

Logistic regression model and Wald test.
*p<0.05.

Table 4. Likelihood of estimated outcome according to sex, beta-blocker and statin use

Sex	Beta blocker	Statin	Probability of MI and myocardial injury
Female	No	Yes	39.2
Male	No	Yes	55.6
Female	Yes	Yes	56.7
Female	No	No	63.3
Male	Yes	Yes	71.7
Male	No	No	77.0
Female	Yes	No	77.8
Male	Yes	No	87.1

MI: myocardial infarction.
Results expressed as %.

DISCUSSION

According to the Fourth Universal Definition of Myocardial Infarction, PCI-related MI (type 4a) is characterized by cardiac troponin elevation to values over five-fold the upper reference limit in the 99th percentile for patients with normal baseline values, or greater than 20% in those with elevated pre-procedural values. The diagnosis also includes evidence of new ischemic event based on electrocardiographic changes, imaging findings or complications associated with reduced flow during the procedure. These changes should take place within no more than 48 hours of procedure completion.[15,16]

In this study, 10% of patients submitted to PCI at a referral interventional cardiology service suffered MI and 56% myocardial injury. Such adverse events may be related to microcirculatory perfusion compromise in response to embolization or periprocedural changes in epicardial vessel blood flow.[17] Some factors, such as vasoactive agent release, platelet activation and pre-existing myocardial vulnerability, may also be related to injury and elevation of cardiac markers during PCI.[18]

In this study, male sex was associated with higher incidence of MI and myocardial injury. However, higher risk of complications has been reported in the literature in women, following adjustment for age and ethnicity, with no differences between males and females regarding mortality and hospital admission in the mid- and long-term.[19] Differences in endothelial activation and vessel anatomy, hormone factors and clinical presentations among women are thought to be responsible for this disparity.[20-22] Underutilization of effective therapies and delays in seeking medical care are thought to be additional factors associated with increased risk of adverse events in women.[20,23] These justifications show that results may vary according to population characteristics. Hence, findings of this study may have reflected secondary factors excluded from this analysis, such as other comorbidities, vessel characteristics, coronary disease progression time and presence of collateral vessels.

Statin use was an independent protective factor against MI and myocardial injury in elective PCI, regardless of drug type, dosage, or time of use. This finding may be explained by pleiotropic effects of statins, including anti-inflammatory, anti-thrombotic and immunomodulating properties associated with improved endothelial function and lower levels of adhesion molecules.[24,25] Long-term statin therapy is thought to promote atherosclerotic plaque stability by increasing the thickness of the fibrous capsule. Reduction of cell aggregate formation and inhibition of thrombosis and coagulation mechanisms are thought to contribute to lower the risk of microvascular obstruction during PCI.[26,27] The pathophysiological mechanism underlying these effects may involve statin-induced reduction in metalloproteinase secretion by macrophages, reduced levels of inflammatory molecules, such as interleukins and tumor necrosis factor, and increased expression of nitric oxide synthase,

leading to enhanced myocardial protection and lower risk of myocardial necrosis marker elevation after stent placement.[6,12,28-31]

Findings limited to the group of patients using statins and beta-blockers in this sample may have been impacted by other confounding variables, including comorbidities requiring beta-blocker use that were not assessed in this study. Heart failure with reduced ejection fraction is one such example, and has been deemed as a risk factor for adverse events during PCI in several studies.[32,33]

This study has some limitations. Firstly, observational cross-sectional design precluded long-term follow-up of patients. Hence, comorbidities potentially impacting MI and myocardial injury outcomes, such as anatomical features of vessels, disease progression time, and medication type and doses were not assessed. Late morbidity and mortality rates were also not investigated. Finally, age and ethnicity were not accounted for in outcome assessment according to sex.

CONCLUSION

Periprocedural myocardial infarction and injury are common outcomes following elective percutaneous coronary intervention and statin pretreatment is an independent protective factor. Male sex was associated with increased incidence of such complications. Findings of this study support positive effects of statins in cardiovascular protection, reinforcing the need to prescribe these drugs based on current evidence.

SOURCE OF FINANCING

None.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: GGP and JK; data collection: GGP, LG, LSD and SK; data interpretation: GGP, JK, LG, LSD, MO and SK; writing of the text: LG, LSD and SK; approval of the final version to be published: GGP, JK, LG, LSD, MO and SK.

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