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Percutaneous intervention in unprotected left main coronary artery lesions

Intervenção percutânea em lesões de tronco de coronária esquerda não protegido

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ABSTRACT – **Background:** The opportunity for percutaneous treatment of coronary artery disease in unprotected left main artery has increased. This treatment possibility is based on favorable results in the literature. The objective of this study was to compare the demographic profile and results of percutaneous coronary intervention in patients with unprotected left main coronary artery lesions. **Methods:** The period from 2006 to 2016 was analyzed, divided into three intervals - 2006 to 2008, 2009 to 2011 and 2012 to 2016, based on the database of the *Central Nacional de Intervenções Cardiovasculares* (CENIC). We verified, in the sample, the influence of variables of interest in relation to mortality. **Results:** A total of 767 patients were included. Clinical, angiographic and procedural characteristics changed throughout the decade analyzed, mostly regarding greater use of drug-eluting stents. There was no difference in mortality or major adverse cardiovascular events. Acute clinical presentation, left ventricular dysfunction, hemodynamic instability or multivessel coronary artery disease were predictors of mortality by logistic regression analysis. **Conclusion:** The use of drug-eluting stents to address the unprotected left main coronary artery has increased in contemporary practice. Although no differences were found in cardiac event rates among the periods, it was noted that emergency procedures in unstable patients, patients with left ventricular dysfunction or with multivessel coronary artery disease remained as important predictors of mortality in this challenging scenario.

Keywords: Coronary disease; Angioplasty; Drug-eluting stents; Myocardial revascularization; Percutaneous coronary intervention

RESUMO – **Introdução:** Cresce a possibilidade de tratamento percutâneo da doença arterial coronária em tronco de coronária esquerda não protegido. Tal conduta é baseada em resultados favoráveis na literatura. O objetivo do presente estudo foi comparar o perfil demográfico e os resultados da intervenção coronária percutânea de pacientes com lesão em tronco de coronária esquerda. **Métodos:** Foi considerado o intervalo de 2006 a 2016, dividido entre os períodos de 2006 a 2008, 2009 a 2011 e 2012 a 2016, com base no banco de dados da Central Nacional de Intervenções Cardiovasculares (CENIC). Buscou-se verificar a influência de variáveis de interesse em relação à mortalidade na amostra. **Resultados:** Foram incluídos 767 pacientes. As características clínicas, angiográficas e dos procedimentos sofreram alterações ao longo da década analisada, com destaque para maior utilização de stents farmacológicos. Não houve diferença em mortalidade ou eventos cardiovasculares adversos maiores. Apresentação clínica aguda, disfunção ventricular esquerda, instabilidade hemodinâmica ou coronariopatia multiarterial foram preditores de mortalidade pela análise de regressão logística. **Conclusão:** A adoção de stents farmacológicos na abordagem do tronco de artéria coronária esquerda não protegido aumentou na prática contemporânea. Embora não se tenham constatado diferenças nas taxas de eventos cardíacos entre os períodos, verificou-se que procedimentos emergenciais em pacientes instáveis, com disfunção ventricular esquerda ou portadores de coronariopatia multiarterial permanecem como importantes preditores de mortalidade nesse cenário desafiador.

Descritores: Doença das coronárias; Angioplastia; Stents farmacológicos; Revascularização miocárdica; Intervenção coronária percutânea

BACKGROUND

In recent years, the possibility of treating coronary disease in the unprotected left main coronary artery (LMCA) by percutaneous coronary intervention (PCI)

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has increased. This management is based on favorable results from randomized clinical trials and registries comparing outcomes of PCI and coronary artery bypass grafting (CABG).[1-3] In fact, recent guidelines recommend PCI in patients with lesions in LMCA and favorable coronary anatomy, that is, with no diffuse and complex lesions.[4]

CABG is still the therapeutic option to address the unprotected LMCA in several situations. In 2016, the NOBLE (Nordic-Baltic-British Left Main Revascularization Study), demonstrated that, despite similar mortality rates, the 5-year risk of major adverse cardiovascular events (MACE) was higher after PCI as compared to CABG.[5] In 2016, Nerlekar et al. published a meta-analysis limited to randomized clinical trials and found no differences in the results regarding clinical safety when comparing PCI using drug-eluting stents and CABG, in low surgical risk patients. In their conclusions, however, they stated CABG is a more effective strategy for revascularization, since PCI is associated with significantly higher rates of repeat revascularization and myocardial infarction in the long-term follow-up.[6]

PCI seems to be equivalent to CABG as to mortality in patients with coronary artery disease in unprotected LMCA. In non-diabetic patients with lower anatomical complexity (SYNTAX score ≤32), PCI is a reasonable alternative to CABG, especially for ostial or mid-shaft lesions in LMCA. CABG is preferable in cases of diabetes, multivessel coronary artery disease or complex lesions (SYNTAX score >33), including distal bifurcation involvement.[7]

The objective of this study was to compare clinical and angiographic profiles and the results of patients with unprotected LMCA lesion submitted to PCI.

METHODS

The study was approved by the Internal Review Board of the *Hospital de Urgências de Goiânia*, under protocol CAAE: 85497418.2.0000.0033. Information was collected from the database of *Central Nacional de Intervenções Cardiovasculares* (CENIC; http://www.corehemo.net/), and official body of the *Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista* (SBHCI). CENIC is a registry of voluntary contribution, the input being provided by participating centers authorized to carry out PCI. The period considered in this study was 2006 to 2016. The clinical and angiographic characteristics of patients with unprotected LMCA lesions submitted to PCI procedures were listed. The interventional procedures performed, the in-hospital clinical outcomes, and the influence of variables of interest regarding mortality were also characterized.

The vessel flow before the procedure was defined by the Thrombolysis in Myocardial Infarction (TIMI) score. Patients with acute clinical presentation were classified as ST- segment elevation myocardial infarction (STEMI) or non-ST segment elevation acute coronary syndrome (NTSE-ACS). Multivessel coronary artery disease was defined as ≥50% stenosis in more than one main epicardial vessel. Thrombotic lesions were defined as those presenting images suggestive of thrombi in angiography. Left ventricular dysfunction was defined as ventricular ejection fraction <40%. The procedural success was considered <20% residual stenosis with no MACE, which included death (cardiac or non-cardiac), myocardial infarction (MI) or emergency revascularization procedures. Death was defined as all cardiac deaths, excluding those in which a non-cardiac cause was identified as the reason for the fatal event.

Statistical analysis

Data from patients with unprotected LCMA lesion submitted to PCI during the period 2006 to 2016, registered in the CENIC registry, were used. The period was divided into three intervals - 2006 to 2008, 2009 to 2011, and 2012 to 2016. The Chi-squared test was used to compare continuous variables. Whenever necessary, the likelihood ratio test was employed. The analysis of variance (ANOVA) was used for comparison of categorical variables, and the Bonferroni correction method for multiple comparisons. In order to verify the influence of variables of interest in relation to mortality, the simple logistic regression model was used, and the 95% confidence interval was calculated. For all analyses, a significance level of 5% ($p < 0.05$) was set. The software Stata©, version 15.1 (StataCorp, Texas, USA) was used.

RESULTS

The sample consisted of 767 patients, with a mean of 1.01 procedure per patient, totaling up 772 interventions. The number of vessels treated was 815, of which 770 (94.5%) had stent deployment (798), a ratio of 1.04 stent/patient. The baseline characteristics of the sample are presented in table 1. There was a significant difference between the periods in the variables smoking, clinical presentation, and history of previous PCI in the interval from 2012 to 2016.

The angiographic characteristics are depicted in table 2. Thrombotic and calcified lesions were more frequent in the period from 2006 to 2008. Table 3 presents the characteristics of the procedures. A higher proportion of treated vessels/patient, stents/patient, use of drug-eluting stents or longer devices was observed from 2012 to 2016. Primary PCI or the prevalence of TIMI flow 0/1 before the intervention were more often reported in the 2006-2008 period.

In-hospital clinical outcomes are listed in Table 4. No significant difference was found in the events studied. By simple logistic regression analysis (Table 5), the clinical presentation of AMI increased, by 18.8 and 28.5-fold, the risk of death when compared to symptomatic stable disease or silent ischemia, respectively. Hemodynamic instability, multivessel coronary artery disease, or left ventricular dysfunction are also predictive variables of in-hospital mortality.

Table 1. Clinical characteristics

Characteristic	2006-2008 (n=181 patients)	2009-2011 (n=261 patients)	2012-2016 (n=325 patients)	p-value
Age, years	66±12.2	65.8±12.7	66.8±12.5	0.590
Male sex	121 (66.9)	154 (59.0)	203 (62.5)	0.246
Smoking	50 (27.6)	38 (14.6)	49 (15.1)	0.0004
Hypertension	144 (79.6)	193 (73.9)	256 (78.8)	0.273
Dyslipidemia	104 (57.5)	131 (51.0)	178 (55.3)	0.368
Diabetes mellitus	39 (21.5)	43 (18.8)	59 (26.6)	0.133
Prior MI	28 (15.5)	26 (11.4)	34 (15.3)	0.371
Prior PCI	31 (17.1)	40 (15.6)	79 (25.0)	0.011
Clinical presentation				0.010
Stable angina	81 (44.8)	101 (38.7)	133 (40.9)	
Silent ischemia	14 (7.7)	31 (11.9)	52 (16.0)	
STEMI	42 (23.2)	50 (19.2)	42 (12.9)	
NSTE-ACS	44 (24.3)	79 (30.3)	98 (30.2)	
Killip				<0.0001
1	13 (31.0)	20 (40.0)	15 (35.7)	
2	2 (4.8)	8 (16.0)	6 (14.3)	
3	4 (9.5)	4 (8.0)	4 (9.5)	
4	23 (54.8)	18 (36.0)	17 (40.5)	

Results presented as mean ± standard deviation, or n (%). MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; NSTE-ACS: non-ST segment elevation acute coronary syndrome.

Table 2. Angiographic characteristics

Characteristic	2006-2008 (n=181 procedures/ n=193 vessels)	2009-2011 (n=264 procedures/ n=269 vessels)	2012-2016 (n=327 procedures/ n=353 vessels)	p-value
Type B2/C lesions	133 (76.4)	264 (100.0)	327 (100.0)	0.141
Calcified lesions	58 (30.1)	71 (27.1)	60 (18.5)	0.005
Thrombotic lesions	29 (15.0)	44 (16.4)	23 (6.5)	0.0002
Long lesions (>20mm)	23 (11.9)	28 (10.4)	31 (8.8)	0.494
Bifurcations	60 (31.1)	100 (37.2)	137 (38.8)	0.191
Total occlusions	28 (14.5)	29 (10.8)	34 (9.7)	0.225
TIMI flow pre				0.009
0/1	41 (21.2)	60 (22.3)	48 (13.6)	
2/3	152 (78.8)	209 (77.7)	305 (86.4)	
Left ventricular dysfunction	76 (55.5)	71 (55.9)	92 (60.9)	0.581
Collateral circulation	23 (13.8)	20 (15.9)	15 (9.8)	0.303

Results presented as n (%). TIMI: *Thrombolysis in Myocardial Infarction.*

Table 3. Characteristics of procedures

Characteristic	2006-2008 (n=181 procedures/ n=180 stents)	2009-2011 (n=264 procedures/ n=268 stents)	2012-2016 (n=327 procedures/ n=350 stents)	p-value
Treated vessels/patient	1.1±0.2	1 ± 0.2	1.1±0.3	0.022
Use of stent	168 (92.8)	252 (96.6)	303 (93.2)	0.145
Stent/patient ratio	1.1±0.3	1.1±0.3	1.2±0.4	0.002
Drug-eluting stents	51 (28.3)	114 (42.5)	187 (53.6)	<0.0001
Stent diameter, mm	3.45±0.65	3.51±0.61	3.5±0.58	0.657
Stent length, mm	16.2±5.9	18.7±9.2	19.1±9.4	0.001
Types of intervention				0.046
Primary PCI	34 (18.8)	41 (15.5)	33 (10.1)	
Rescue PCI	3 (1.7)	3 (1.1)	2 (0.6)	
GP IIb/IIa inhibitors	19 (10.5)	20 (7.6)	9 (2.8)	0.001
Thromboaspiration	0 (0)	2 (0.7)	2 (0.6)	0.346
TIMI flow post				<0.0001
0/1	32 (17.8)	17 (6.3)	11 (3.1)	
2/3	148 (82.2)	251 (93.7)	339 (96.9)	
Diameter stenosis				
Pre	83.4 (15.4)	86 (39.8)	80.2 (18.0)	0.029
Post	5.6 (17.1)	5 (16.5)	4.8 (9.4)	0.821
Success of procedure	157 (86.7)	238 (90.2)	299 (91.4)	0.239

Results presented as mean ± standard deviation, or n (%). PCI: percutaneous coronary intervention; GP: glycoprotein; TIMI: *Thrombolysis in Myocardial Infarction.*

Table 4. In-hospital clinical outcomes

Outcome	2006-2008 (n=181 patients)	2009-2011 (n=261 patients)	2012-2016 (n=325 patients)	Total (n=767 patients)	p-value
MI	2 (1.1)	4 (1.7)	3 (1.4)	9 (1.4)	0.857
Emergency CABG	0	2 (0.9)	1 (0.5)	3 (0.7)	0.810
Death	21 (11.6)	15 (6.6)	22 (8.9)	58 (8.8)	0.201
MACE	21 (11.6)	20 (7.7)	24 (7.4)	65 (8.5)	0.223

Results presented as n (%). MI: myocardial infarction; CABG: coronary artery bypass surgery; MACE: major adverse cardiovascular events.

Table 5. Influence of variables of interest regarding mortality by simple logistic regression

Variable	Estimate	p-value	OR	95%CI
2009-2011 vs. 2006-2008	-0.63	0.076	0.53	0.27-1.07
2012-2016 vs. 2006-2008	-0.30	0.353	0.74	0.39-1.39
Age, years	-0.01	0.539	0.99	0.97-1.01
Sex, female vs. male	0.10	0.727	1.10	0.64-1.91
Smoking, no vs. yes	0.16	0.656	1.18	0.58-2.39
Diabetes mellitus, yes vs. no	-0.20	0.578	0.82	0.4-1.67
Prior acute MI, yes vs. no	0.43	0.252	1.53	0.74-3.18
Stable angina vs. STEMI	-2.93	<0.0001	0.05	0.02-0.13
Silent ischemia vs. STEMI	-3.35	0.001	0.04	0-0.26
NSTE-ACS vs. STEMI	-2.14	<0.0001	0.12	0.06-0.24
Killip, 1 vs. 4	-1.61	0.0006	0.20	0.08-0.5
Killip, 2 vs. 4	-2.64	0.013	0.07	0.01-0.58
Killip, 3 vs. 4	-1.10	0.125	0.33	0.08-1.36
Left ventricular dysfunction, yes vs. no	1.89	0.002	6.64	1.97-22.35
Collateral circulation, yes vs. no	0.40	0.368	1.49	0.63-3.55
Primary PCI vs. others	2.63	<0.0001	13.82	7.6-25.15
Rescue PCI vs. others	1.32	0.228	3.74	0.44-31.83

MI: myocardial infarction; STEMI: ST segment elevation myocardial infarction; NSTE-ACS: non-ST segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention.

DISCUSSION

In selected patients, PCI is a safe and durable method for the treatment of lesions in unprotected LMCA, being an alternative to CABG, as corroborated by meta-analyses about this topic.[8,9] However, in current practice, CABG is preferred by the clinical teams. With the current pharmacotherapy and advances in both surgical and percutaneous treatments, longer follow-up of the patients is required to establish similarities of the techniques.[10]

In the FREEDOM trial,[11] which included 1,900 diabetic patients with multivessel disease who were randomized for PCI with drug-eluting stent or CABG, with a mean follow-up of 3.8 years, the rate of MI was higher in patients submitted to PCI as compared to CABG (13.9% vs. 6.0%, p<0.001). An important limitation is the follow-up time, given the long-term durability of surgical grafts, particularly non-arterial grafts. While 5-year patency has been well established, greater failure of venous grafts is verified between 10 and 15 years. In addition, first-generation drug-eluting stents were primarily used.[12]

The optimization of LMCA revascularization is critical, since this vessel supplies up to 75% of the left ventricular myocardium. Different strategies can be used to improve the outcomes of PCI in unprotected LMCA, including drug-eluting stents. The first studies used devices known to be prone to increased risk of thrombotic complications. The advent of the new generation everolimus-eluting stents had a positive impact on the clinical evolution, since the absolute difference in safety and efficacy compared to the previous ones was progressively more pronounced, as the complexity of the lesions increased (for example, high anatomical SYNTAX score).[13]

The DELTA registry has shown that PCI for ostial or mid-shaft lesions in LMCA was associated to clinical outcomes comparable to those seen with CABG in long-term follow-up, despite the use of first generation drug-eluting stents.[14] The in-hospital mortality of DELTA trial was lower than in our investigation, i.e., 2.5% vs. 8.8%, respectively, for all-cause mortality. It is important to remember that most studies excluded patients with MI and cardiogenic shock; however, this fact does not occur in CENIC database, the source of data herein presented.

Naganuma et al. found an association between left ventricular dysfunction and MACE, including death.[15] In our study, this finding was also observed, and the risk of death was approximately six-fold greater in subjects with this presentation. Moreover, an association between mortality and number of diseased vessels was found in our investigation. There is a broad consensus that uncomplicated single or two-vessel coronary artery disease may be treat by PCI, while in the more complex three-vessel disease, CABG is justified.[16,17] However, some factors, such as site of the lesion, degree of stenosis or calcification, also play a key role when making clinical decisions.[18] We also found a lower risk of death for patients with prior PCI. This could be explained in part by the fact that patients already submitted to PCI receive better medical follow-up, minimizing the negative consequences attributed to cardiovascular risk factors.

Patients should be given all relevant pieces of information to make a sound decision about the ideal revascularization approach. According to the guidelines of the European Society of Cardiology (ESC), the most valuable recommendation is provided by the heart team, who plays an important role in decision making, sharing it among different healthcare professionals, patients and family members.[17] It is important that the physician be acquainted with the current guidelines that specify recommendations regarding LMCA revascularization based on anatomical complexity.[19] For patients with LMCA disease and SYNTAX score <22, CABG and PCI are included in class I-B recommendations. For patients with LMCA disease and SYNTAX score 22 to 32, CABG receives class I-B recommendation, while PCI receives class IIa-B recommendation. For patients with LMCA disease and SYNTAX score >32, CABG receives recommendation class I-B, while PCI, recommendation class III-B.

In favor of PCI, Coughlan et al. provided evidence that procedures with current drug-eluting stents are a treatment option for unprotected LMCA lesions in centers with no local surgical support, particularly in emergency cases, such as STEMI and cardiogenic shock, as well as in patients at very high risk for CABG.[20] Stone et al. suggested PCI with everolimus-eluting stents is an acceptable or even preferred alternative to CABG in selected patients with LMCA disease.[21] Analysis of the EXCEL study (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) suggested approximately 62% of patients with LMCA lesions were eligible for PCI, and roughly 80% able for CABG. Once again, decisions related to revascularization should be made after discussion among the heart team members, taking into account the individual circumstances, expectations and preferences of each patient.

This study has important limitations that must be highlighted. It is a retrospective study, whose findings are derived from a database of voluntary contributions, subject to errors related to the data input on the CENIC platform, with no systematic evaluation of the outcomes.

CONCLUSION

The adoption of drug-eluting stents in the approach of the unprotected left main coronary artery has increased over the years, as well as stent length. In the sample assessed, no differences were found in clinical outcomes throughout a decade. Acute clinical presentation, left ventricular dysfunction or multivessel coronary artery disease were associated to higher mortality rates in this challenging scenario.

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None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

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