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Resultados de um Programa de Tratamento Percutâneo de Lesões do Tronco Comum

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Resultados de Um Programa de Tratamento Percutâneo de Lesões do Tronco Comum

Results of a Percutaneous Treatment Program of Left Main Disease

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Table of contents

Abstract 4
Resumo 6
Introduction 8
Materials and Methods 10
Study design and setting 10
Participants 10
Data collection 10
Data registration and Statistical methods 10
Results 12
Discussion 18
Comparison with the literature 18
Limitations 20
Conclusion 21
Acknowledgements 22
References 23
Appendix 26

Abstract

Introduction: Left main coronary artery (LMCA) disease is associated with a high risk of cardiovascular events. Currently, the preferred method of treatment is coronary artery bypass graft (CABG), but several studies suggest that percutaneous coronary intervention (PCI) is a viable alternative.

Objective: We aimed to evaluate the efficacy and security of PCI procedures used for the treatment of LMCA disease in Centro Hospitalar e Universitário de Coimbra (CHUC).

Methods: Observational, retrospective study including patients submitted to a PCI procedure for the treatment of LMCA disease between January 2015 and December 2019, excluding ST-segment elevation myocardial infarction (STEMI) patients. Patients were divided according to their SYNTAX score. We made a global analysis of the clinical and angiographic data. Also, we analyzed the influence of the SYNTAX score and other clinical and angiographic variables in the clinical outcomes (all-cause mortality, myocardial infarction, cerebrovascular events, need for CABG after PCI procedure and a composite outcome of all-cause mortality or myocardial infarction) of the patients.

Results: A total of 122 patients were enrolled in this study (median age 72 [65-82] years, 96 (78.7%) males), with 57 patients (46.7%) in the Low, 33 (27.1%) in the Intermediate and 32 (26.2%) in the High SYNTAX score group. Median follow-up time were 770 [425-1294] days. There were statistical differences between the Low and High SYNTAX score groups in diabetes mellitus frequency (p<0.01), and between the Low and the other two groups in preserved left ventricular ejection fraction (LVEF) presence (p=0.02 for Intermediate and p=0.04 for High) and in the lesion localization (p<0.01 for Intermediate and p=0.02 for High). There were also significant differences in the number of deaths between the Low and High SYNTAX score groups (p<0.01). Survival analysis showed significant differences between the and low SYNTAX score groups in all-cause mortality and the composite outcome of all-cause mortality or myocardial infarction (p<0.01 for both outcomes). Multivariate analysis showed that insulin-treated diabetes mellitus (ITDM) (HR=2.44, CI 1.02-9.51 p=0.04), atrial fibrillation (AF) (HR=2.60 CI 1.03-6.61 p=0.04) and valvular heart disease (VHD) (HR=2.64, CI 1.02-6.83 p=0.04) were independent predictors for the occurrence of the composite outcome of all-cause mortality or myocardial infarction.

Conclusions: Patients with Low SYNTAX scores presented lower rates of all-cause mortality and occurrence of the composite outcome of all-cause mortality or myocardial infarction than

the High SYNTAX score group. ITDM, AF and VHD were associated with higher rates of death or myocardial infarction.

Keywords: Left Main; Percutaneous Coronary Intervention; Coronary Artery Disease

Resumo

Introdução: A doença coronária do tronco comum (DTC) está associada com um elevado risco de eventos cardiovasculares. Atualmente, o método de eleição para o seu tratamento é a cirurgia de bypass coronário (CABG), mas vários estudos sugerem que a intervenção coronária percutânea (ICP) é uma alternativa viável.

Objetivo: Avaliar a eficácia e segurança dos procedimentos de ICP realizados para o tratamento de DTC no Centro Hospitalar e Universitário de Coimbra.

Métodos: Estudo observacional, retrospetivo que incluiu doentes submetidos a uma ICP para tratamento de DTC entre janeiro de 2015 e dezembro de 2019, excluindo doentes com enfarte agudo do miocárdio com elevação do segmento ST. Os doentes foram divididos de acordo com o seu score SYNTAX. Realizou-se uma análise global dos dados clínicos e angiográficos. Também se analisou a influência do score SYNTAX e de outras variáveis clínicas e angiográficas nos *outcomes* clínicos (mortalidade, enfarte do miocárdio, eventos cerebrovasculares, necessidade de CABG após o procedimento de ICP e um *outcome* composto de morte ou enfarte do miocárdio) dos doentes.

Resultados: Foram incluídos 122 doentes no estudo (idade mediana 72 [65-82] anos, 96 (78.7%) homens), com 57 (46.7%) doentes com score SYNTAX Baixo, 33 (27.1%) com score Intermédio e 32 (26.2%) com score Alto. O tempo mediano de seguimento foi de 770 [425-1294] dias. Houve diferenças significativas entre os doentes com score Baixo e Alto na frequência de diabetes mellitus (p<0.01), e entre os doentes com score Baixo e os restantes grupos na presença de fração de ejeção preservada (p=0.02 e p=0.04 no grupo Intermédio e Alto, respetivamente) e na localização da lesão (p<0.01 e p=0.02, no grupo Intermédio e Alto, respetivamente). Também houve diferenças significativas entre doentes com score Baixo e Alto no número de mortes (p<0.01). A analise de sobrevivência mostrou diferenças significativas entre os grupos com score Baixo e Alto na mortalidade e no *outcome* composto de morte ou enfarte do miocárdio (p<0.01 em ambos). A análise multivariada mostrou que a diabetes insulino-tratada (DMIT) (HR=2.44, CI 1.02-9.51 p=0.04), a fibrilhação auricular (FA) (HR=2.60 CI 1.03-6.61 p=0.04) e a doença valvular cardíaca (HR=2.64, CI 1.02-6.83 p=0.04) eram preditores independentes da ocorrência do *outcome* composto de morte ou enfarte do miocárdio.

Conclusões: Doentes com scores SYNTAX baixos apresentaram menores taxas de mortalidade e de ocorrência do outcomes composto de morte ou enfarte do miocárdio. A

DMIT, a FA e a doença valvular cardíaca estão associadas com maiores taxas de morte ou enfarte do miocárdio.

Palavras-chave: Tronco comum; Intervenção Coronária Percutânea; Doença Coronária

Introduction

The left main coronary artery (LMCA) is the first segment of the left coronary artery. Usually, it arises from the left aortic sinus and after a mean length of approximately 10 mm, it bifurcates into the left circumflex artery and left anterior descending artery (in some patients, an intermediate branch may arise at the termination).[1-3] This artery is responsible for providing blood supply to more than 75% of the left ventricular myocardium (which can rise to 100% depending on the dominance of the left coronary circulation), which puts LMCA disease at a higher risk of cardiovascular events.[1-4]

Around 4% to 6% of coronary angiograms show obstructive LMCA disease,[1, 3, 5] and only 5 to 10% correspond to isolated disease.[1, 3, 5] LMCA disease can be categorized in ostial, mid-shaft or distal.[1] Lateral walls of the bifurcation are the most commonly affected area by atherosclerotic disease.[1-3]

Clinically, unprotected left main artery disease can present in several ways, ranging from asymptomatic to sudden death, but the most common manifestation is stable angina. Artery occlusion often leads to hemodynamic instability, and mortality can reach 70% in the first 24 hours.[2]

Relying on clinical features, it is not possible to fully predict the presence of LMCA. Coronary angiography is the main tool to assess left main artery disease.[2] Intravascular ultrasound (IVUS) and fraction flow reserve measurements are considered when angiography is inconclusive.[1, 2]

According to European guidelines, myocardial revascularization is recommended in patients with stenosis greater than 50%.[6] The preferred method of revascularization has been the cardiac artery bypass grafting surgery (CABG), which is a class I recommendation regardless of the SYNTAX score.[4, 6] However, with the advances in percutaneous coronary intervention (PCI), multiple studies attempted to show that this method could have similar results to CABG in the treatment of LMCA. The EXCEL[7] and the NOBLE[8] trials are the main studies on this topic, and their results were contradictory. While in the EXCEL study PCI proved to be non-inferior to CABG in patients with low to intermediate anatomic complexity (measured by SYNTAX score),[1, 7] in the NOBLE trial, CABG outperformed PCI in all groups, regardless of the patients' SYNTAX score.[1, 8] A more recent meta-analysis showed that PCI was associated to lower mortality in patients with low SYNTAX scores contrasting to a higher mortality in those with higher SYNTAX scores.[1]

With the present knowledge, current European guidelines consider PCI equivalent to CABG for patients with low angiographic complexity (with SYNTAX scores inferior to 22, to which it has a class I recommendation) and do not recommend PCI in patients with SYNTAX

scores above 32. In those with intermediate scores, there is no clear recommendation due to lack of results in the long term follow-up in previous trials.[6]

This study aims to evaluate the efficacy and security of PCI procedures used to treat LMCA disease in Centro Hospitalar e Universitário de Coimbra (CHUC), according to patient and technical factors.

Materials and Methods

Study design and setting

This is a retrospective, observational study, conducted between November 2020 and February 2021. Ethical approval was obtained from Comissão de Ética do Centro Hospitalar e Universitário de Coimbra. Data was obtained from patients' emergency department and hospitalization registries.

Participants

In this study, we included patients submitted to a percutaneous coronary intervention to treat left main coronary artery disease between 2015 and 2019 in Centro Hospitalar e Universitário de Coimbra. Patients with a STEMI diagnosis were excluded. A total of 122 patients were enrolled in this study.

Data collection

Data collected was registered with the anonymity of the patients assured by irreversible anonymization of the data. For this study, clinical, angiographic and outcome related variables were considered.

The clinical variables included age, gender, body mass index (IMC), smoking history, diabetes mellitus (treated with insulin or not), arterial hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), atrial fibrillation, valvular heart disease (VHD), chronic kidney disease, history of previous myocardial infarctions, history of previous PCI and left ventricular ejection fraction (LVEF).

The angiographic variables considered were SYNTAX score, lesion localization (non-distal, which included ostial and midshaft lesion, and distal), degree of lesion stenosis, use of intravascular imaging for lesion evaluation, use of physiology evaluation methods, initial strategy used for treatment and the techniques used for bifurcation disease treatment and lesion preparation.

The outcome variables comprised the length of follow-up care, in-hospital and all-cause mortality, cause of death, incidence of myocardial infarction (MI) and cerebrovascular events after PCI and the need for CABG following the PCI procedure.

Data registration and Statistical methods

Patients were divided according to their SYNTAX score into three groups: low (SYNTAX below 22), intermediate (between 23 and 32) and high (above 33) SYNTAX score.

We evaluated statistical differences between groups using the Chi-square test and median comparison test for categorical and numerical variables, respectively. Survival analysis was assessed by Kaplan Meier estimate and Cox regression test.

The Kaplan Meier estimate was made for each SYNTAX score group regarding all-cause death, myocardial infarction, cerebrovascular events, need for CABG after the procedure and a composite endpoint combining all-cause mortality and myocardial infarction. Statistical differences were evaluated using log-rank test.

In the Cox regression analysis, the endpoint considered was the composite of all-cause mortality and myocardial infarction. A multivariate model was created using significant clinical and angiographic variables identified in the univariate analysis for the previously mentioned endpoint. A Kaplan Meier estimate was made for each independent predictor found in the multivariate analysis.

Analyses were performed using IBM SPPS Statistics for Windows V.26.0 and values of $p < 0.05$ were considered statistically significant.

Results

A total of 122 patients were enrolled in this study. The median age of the participants was 72 years [65-82] and 96 (78.7%) were male. From the 122 patients, 57 (46.7%) had low SYNTAX score, 33 (27.1%) had Intermediate SYNTAX score and 32 (26.2%) had high SYNTAX score.

The clinical and angiographic characteristics of the participants, divided by their SYNTAX score, are shown in **Table 1** and **Table 2**.

Significant statistical differences between groups were found in diabetes mellitus (p=0.02*)*, the presence of preserved LVEF (p=0.03) and lesion localization (p<0.01).

In diabetes mellitus, significant differences were found between the Low SYNTAX and the High SYNTAX score groups (p<0.01) and no difference was found between the Intermediate SYNTAX score group and the other two groups (p=0.28 and p=0.12 for the low and high group, respectively).

Regarding preserved LVEF, significant differences were found between the Low SYNTAX score and the other two groups, with p=0.02 between Low and Intermediate groups and p=0.04 between Low and High groups. No significant differences were found between the Intermediate and High groups (p=0.80)

In the lesion localization, significant differences were found between the Low and Intermediate groups (p<0.01) and the Low and High groups (p=0.02). No significant differences were found between the Intermediate and High SYNTAX score groups (p=0.42).

The median follow-up time of the patients was 770 days [425-1294], and 3 patients were lost to follow-up during the period of the study. Other follow-up data is present in **Table 3**.

Significant statistical differences between groups were found in all-cause mortality (p=0.02). Considering the frequency of this event, significant differences were found between the Low and High SYNTAX score groups (p<0.01), with no significant differences between the Low and Intermediate (p=0.43) and Intermediate and High (p=0.81) SYNTAX score groups.

Table 1. Baseline clinical characteristics stratified by SYNTAX score

	All patients (n = 122)	**Low SYNTAX score (n=57)**	**Intermediate SYNTAX score (n = 33)**	**High SYNTAX score (n =32)**	***p* value**
Age – yr	72 [65-82]	72 [64-82]	76 [61-84]	73 [71-78]	0.45
Male gender	96 (78.7%)	41(71.9%)	30 (90.9%)	25 (78.1%)	0.11
Clinical characteristics					
Hypertension	110 (90.2%)	52 (91.2%)	28 (84.9%)	30 (93.8%)	0.45
DM	58 (47.54%)	21 (36.8%)	16 (48.5%)	21 (65.6%)	**0.02***
ITDM	23 (18.9%)	9 (15.8%)	4 (12.1%)	10 (31.3%)	0.09
Dyslipidemia	114 (93.4%)	53 (93.0%)	31 (93.9%)	30 (93.8%)	0.77
Smoking history	38 (31.2%)	16 (28.1%)	12 (36.4%)	10 (31.3%)	0.88
BMI	27.68 [25.71-31,20]	27.06 [25.63-31.02]	28.03 [25.2-31.59]	28.34 [26.13-33.00]	0.22
AF	20 (16.4%)	8 (14,0%)	5 (15.2%)	7 (21.9%)	0.54
CKD	31 (25.4%)	15 (26.3%)	7 (21.2%)	9 (28.1%)	0.76
COPD	7 (5.7%)	4 (7.0%)	2 (6.1%)	1(3.1%)	0.77
Significant VHD[1]	30 (24.6%)	14 (24.6%)	9 (27.3%)	7 (21.9%)	0.87
Prior MI	36 (29.5%)	14 (24.6%)	10 (30.3%)	12 (37.5%)	0.38
Prior PCI	40 (32.8%)	19 (33.3%)	8 (24.2%)	13 (40.6%)	0.37
LVEF (≥ 50%)	56 (45.9%)	33 (57.9%)	10 (30.3%)	13 (40.6%)	**0.03***

Values are expressed in mean± SD, median [IQ] or number/total (%),
DM – Diabetes Mellitus; **ITDM –** Insulin-treated Diabetes Mellitus; **BMI** – Body mass index; **AF** – Atrial fibrillation; **CKD** – Chronic Kidney disease; **COPD** – Chronic Obstructive Pulmonary disease; **VHD** – Valvular Heart disease; **LVEF** – Left ventricular ejection fraction; **MI** – myocardial infarction; **PCI** – Percutaneous coronary intervention.
1-Significant VHD was considered in patients with, at least, moderate VHD.

Table 2. Baseline angiographic characteristics stratified by SYNTAX score

	Total	Low SYNTAX score	Intermediate SYNTAX score	High SYNTAX score	*p* value
Lesion localization					**<0.01***
Non distal	30 (24.6%)	22 (38.60%)	3 (9.1%)	5 (15.6%)	
Distal	92 (75.4%)	35 (61.4%)	30 (90.9%)	27 (84.4%)	
Intravascular imaging	40 (32.8%)	24 (42.1%)	10 (30,30%)	6 (18.8%)	0.07
Physiology evaluation	2 (1.6%)	1 (1.8%)	1 (3.0%)	0	0.63
Initial strategy					0.81
Provisional stenting	60 (49.2%)	24 (42.1%)	20 (60.6%)	16 (50.0%)	
Final Kissing-ballon	19 (15.6%)	8 (14.0%)	7 (21.2%)	4 (12.5%)	0.79
Two stent strategy	37 (30.3%)	13 (22.8%)	12 (36.4%)	12 (37.5%)	
Type of two stent strategy					0.33
T-stent/TAP	7 (5.7%)	4 (7.0%)	1 (3.0%)	2 (6.3%)	
Cullote	16 (13.1%)	4 (7.0%)	7 (21.2%)	5 (15.6%)	
DK crush	4 (3.3%)	2 (3,5%)	2 (6.1%)	0	
Mini crush	8 (6.6%)	3 (5.3%)	2 (6.1%)	3 (9.4%)	
Kissing stent	2 (1.6%)	0	0	2 (6.3%)	
Calcium technique					0.15
Rotablator	8 (6.6%)	2 (3.5%)	1 (3,0%)	5 (15.6%)	
Cutting-ballon	7 (5.7%)	3 (5.3%)	3 (9.1 %)	1 (3.1%)	

Values are expressed in mean± SD, median [IQ] or number/total (%).

Table 3. Patients' follow-up stratified by SYNTAX score

		Total	Low SYNTAX score	Intermediate SYNTAX score	High SYNTAX score	*p* value
Follow-up time (days)		770 [425-1294]	801 [503-1387]	798 [533-1170]	611 [213-1270]	0.69
All-cause mortality		35 (28.7%)	11 (19.3%)	9 (27.3%)	15 (46.9%)	**0.02***
In-hospital mortality		4 (3.3%)	1 (1.85%)	1 (3.0%)	2 (6.3%)	0.52
Cause of death	CV	6 (4.9%)	3 (5.3%)	1 (3.0%)	2 (6.3%)	0.70
	Non CV	11 (9.0%)	4 (7.0%)	2 (6.1%)	5 (15.6%)	
	Unknown	18 (14.7%)	4 (7.0%)	6 (18.2%)	8 (25.0%)	
Cerebrovascular event		3 (2,5%)	1 (1.8%)	2 (6.1%)	0	0.30
MI		8 (6.6%)	4 (7.2%)	1 (3.0%)	3 (9.4%)	0.57
Bypass Surgery		2 (1,6%)	1 (1.8%)	1 (3,0%)	0	0.65

Values are expressed in mean± SD, median [IQ] or number/total (%),
CV – Cardiovascular; **MI** – Myocardial infarction

Survival estimation analysis showed significant differences between groups in all-cause mortality (***p*=0.03**) and in the composite outcome of Myocardial infarction or all-cause mortality (***p*= 0.02**). In the previously mentioned outcomes, significant differences between Low SYNTAX score group and High SYNTAX score group were found (***p*<0.01** for both outcomes). No significant differences were found between the Intermediate SYNTAX score group and the other groups in neither of these outcomes (*p*=0.37 and *p*=0.19 between Low and Intermediate score groups and *p*=0.35 and *p*=0.16 between Intermediate and High SYNTAX score groups for all-cause mortality and the composite endpoint, respectively).

There were no significant differences between groups in the survival function test for myocardial infarction (*p*=0.55), cerebrovascular events (*p*=0.32) and need for CABG surgery after PCI (*p*=0.70).

Survival time estimates considering all-cause mortality and the composite outcome of all-cause mortality or myocardial infarction are presented in **Figures 1** and **2**, respectively.

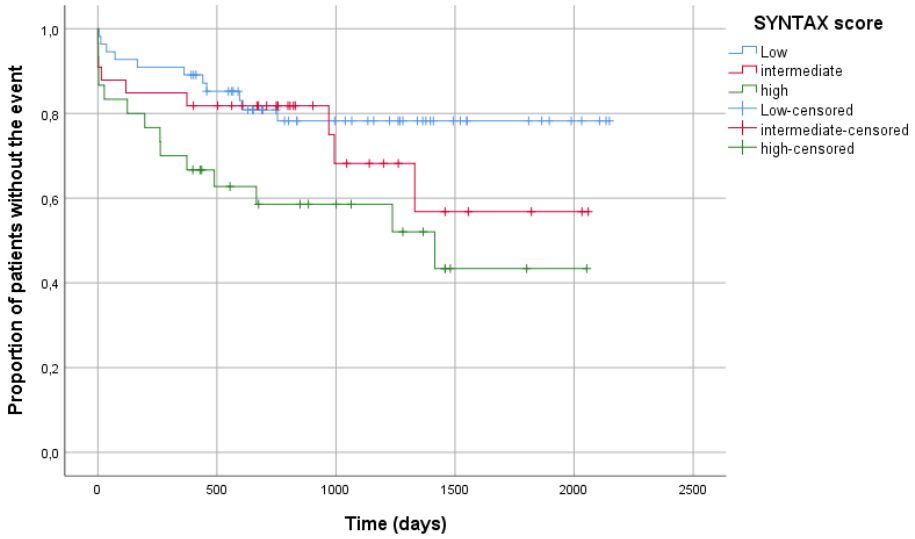

Figure 1. Estimated Survival time for all-cause death according to the SYNTAX score group

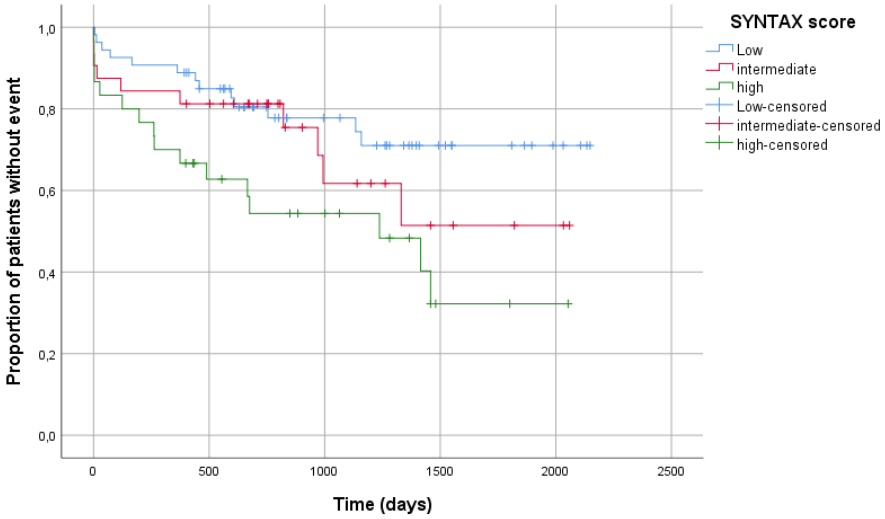

Figure 2. Estimated Survival time for the composite outcome according to the SYNTAX score group.

The multivariate analysis for the composite outcome of Death or Myocardial infarction is presented in **Table 4**. Regarding the clinical and procedural variables with impact in the previous mentioned outcome, insulin treated diabetes (HR=2.44, CI 1.02-9.51 *p*=0.04), atrial fibrillation (HR=2.60 CI 1.03-6.61 *p*=0.04) and valvular heart disease (HR=2.64, CI 1.02-6.83 *p*=0.04) were independent predictors. The survival estimates for insulin treated diabetes, atrial fibrillation and valvular heart disease patients are presented in **Appendix I, II and III,** respectively.

Table 4. Univariate and Multivariate Cox regression analyses of factors with possible influence in the outcome

	Univariate analysis		Multivariate analysis	
	p value	HR (95% CI)	*p* value	HR (95% CI)
	Covariates			
Clinical characteristics				
Age	0.08	1.03 (0.99-1.06)		
Male gender	0.54	0.77 (0.34-1.76)		
Body mass index	0.56	1.02 (0.96-1.08)		
Hypertension	0.14	0.51 (0.22-1.23)		
Diabetes mellitus	0.07	1.83 (0.95-3.54)		
Insulin-treated diabetes	**0.01**	**2.44 (1.24-4.78)**	**0.04**	**3.11 (1.02-9.51) ****
Dyslipidemia	0.30	2.88 (0.39-20.99)		
Smoking history	0.04	2.09 (1.04-4.25)	0.05	2.28 (0.99-5.27)
Chronic kidney disease	<0.01	2.91 (1.48-5.72)	0.52	1.43 (0.49-4.17)
Atrial fibrillation	**<0.01**	**3.19 (1.59-6.39)**	**0.04**	**2.60 (1.03-6.61) ****
Valvular heart disease	**0.01**	**2.44 (1.20-4.93)**	**0.04**	**2.64 (1.02-6.83) ****
Previous MI	0.87	1.51 (0.53-2.10)		
Previous PCI	0.27	0.67 (0.33-1.36)		
LFVE (>50%)	0.01	0.41 (0.20-0.83)	0.30	0.59 (0.22-1.57)
Angiographic and procedure characteristics				
SYNTAX score[1]	0.02	1.03 (1.01-1.06)	0.51	1.01 (0.98-1.05)
Lesion localization (distal)	0.51	1.30 (0.59-2.82)		
Intravascular imaging use	0.11	0.54 (0.26-1.14)		
Initial stent strategy (provisional stent, two-stent)	0.84	0.93 (0.46-1.89)		
Final Kissing balloon (in provisional strategy)	0.16	0.46 (0.51-1.37)		
Calcium technique use	0.28	0.52 (0.16-1.69)		

Data presented with *p* values and hazard ratios for a 95% confidence interval. **HR** – Hazard Ratio, **CI** – Confidence Interval
MI – Myocardial infarction, **PCI** – Percutaneous coronary intervention, **LVEF** – left ventricular ejection fraction.
1-For this analysis, weconsidered the absolute score of the patient and not the group to which the patient belonged.

Discussion

In this study, we aimed to evaluate the PCI procedures for the treatment of LMCA disease in CHUC. We found that diabetes mellitus was less frequent in Low SYNTAX score patients and more common in the High SYNTAX score group, the LVEF was preserved more frequently in the Low SYNTAX group and LMCA lesions were more frequently ostial or mid-shaft in the Low score groups, while in the Intermediate and High score groups lesions were usually distal.

Considering the clinical follow-up, we found out that the High SYNTAX score group had higher mortality rate and occurrence of the composite outcome comparing to the Low SYNTAX score group. Insulin-treated diabetes, atrial fibrillation and valvular heart disease negatively impacted the survival of patients submitted to a PCI for the treatment of LMCA disease.

Comparison with the literature

The population enrolled in this study presented some differences in relation to the NOBLE[8] study population, the main study on LMCA disease that also included High SYNTAX score patients. Our patients had a higher median age of 72 years and a higher incidence of comorbidities such as diabetes, hypertension, and dyslipidemia. Also, the history of previous PCI procedures was more common in our study.

In the SYNTAX score tertile distribution, our study had a similar number of patients to the NOBLE study in the Low SYNTAX score group (46.7% versus 50.1%). However, NOBLE enrolled more patients with an Intermediate SYNTAX score (27.1% versus 42.1%) and our study included more patients in the High SYNTAX score group (26.2% versus 7.8%).

Regarding the outcomes, we had a higher mortality rate comparing to the results obtained after the 5-year follow-up in the NOBLE study[9] (28.7% versus 9%, respectively). However, we had similar rates of known cardiovascular death (4.9% versus 4% in the NOBLE trial) and lower rates of myocardial infarction (6.5% versus 8%) and cerebrovascular events (2.5% versus 4%).

LMCA disease has a great impact in the patients' SYNTAX score, due to the importance of this segment in the vascularization of the heart.[10] More frequently, lesions in the LMCA involve the bifurcation,[1-3] which also increases the anatomic complexity of the disease resulting in higher SYNTAX scores.[10] Therefore, it is not surprising that proximal or midshaft lesions were more common in the low SYNTAX score group than in the intermediate and high SYNTAX score groups.

Patients with low SYNTAX scores had more frequently preserved LVEF comparing to the other groups, which could reflect the lower anatomical complexity of the disease.

Diabetes is a well-known risk factor for vascular disease, increasing the risk of systemic atherosclerosis and advanced coronary disease.[11] The typical diabetic patient with coronary disease presents a higher atherosclerotic burden and a diffuse disease, and usually has longer lesions with high grades of calcification.[12] Considering this factor, it is not surprising that this group presents a more complex coronary anatomy, which could explain the difference in the number of diabetics between the Low SYNTAX score group and the High SYNTAX score group.

In this study, insulin-treated diabetes patients were at a higher risk of death or myocardial infarction compared with non-diabetic and non-insulin treated diabetes patients which goes to the encounter of the findings in other studies.[12] This increased risk may be explained by a more severe form of the disease,[13] which has more vascular damage associated. Other possible explanation is the endothelial dysfunction associated with hyperinsulinemia, since some studies indicate that insulin may be responsible for promoting a proinflammatory vascular state, resistance to antiplatelet agents and platelet dysfunction, which is worsened by the administration of iatrogenic insulin.[12-14]

Our study also suggests an increased risk of death or myocardial infarction in patients with moderate or severe VHD submitted to percutaneous treatment of LMCA disease. In industrialized countries such as Portugal, the most common types of acquired valvular heart disease are aortic stenosis and mitral regurgitation (MR), mainly caused by degenerative changes.[15-17] Calcific aortic stenosis shares several features with atherosclerosis in its early development and progression, including some risk factors,[18, 19] and is associated with a higher risk of cardiovascular events.[19] Aortic stenosis is also associated with left ventricular hypertrophy due to left ventricular pressure overload, that may evolve into heart failure if not treated,[20] and a reduction of the coronary flow reserve, even in patients without coronary heart disease.[21] MR is associated with left-atrial enlargement and with left ventricle changes, which in latter stages of the disease cause left ventricular dysfunction. As such, patients with MI have an increased risk of heart failure and atrial fibrillation.[17]

Coronary artery disease is, currently, the primary risk factor for heart failure[22, 23] that is mainly caused by left ventricular dysfunction,[23] which LMCA disease can potentiate, since this artery is the main responsible for the vascularization of the left ventricle.[1-4] As such, the two most common types of VHD and coronary artery disease are both risk factors for heart failure, that, by itself, is associated with significant morbidity and mortality,[24, 25] and worse outcomes after PCI revascularization.[6, 23] This, along with other comorbidities related to VHD such as atrial fibrillation, could explain the worse outcomes this particular group presents.

In our study, atrial fibrillation increased the risk of death or myocardial infarction in patients submitted to PCI for the treatment of LMCA disease. Atrial fibrillation shares some risk

factors with coronary disease such as diabetes, hypertension and obesity[26] and is, by itself, a risk factor for the development of cardiovascular disease and the occurrence of major cardiovascular events,[27] with some studies indicating a particular relation between AF and a higher risk of LMCA disease. Furthermore, patients with AF and CHD have a higher rate of complications and mortality.[26]

AF also influences the therapeutic decision on the antithrombotic therapy after procedure. Most patients with this arrythmia have indication for the use of anticoagulant therapy to prevent the occurrence of strokes.[28] As such, the combination of these therapies puts this specific subgroup in a higher risk of hemorrhagic events [6] and creates the challenge of balancing the bleeding risk with the ischemic risk.

Considering all these factors, the patient with LMCA disease and AF represents a therapeutic challenge, regardless of the treatment method, since AF is also associated with a higher mortality and morbidity in patients submitted to CABG.[29]

We showed that in the High SYNTAX group, the occurrence of the composite endpoint and mortality were superior to the ones in the low SYNTAX group. This finding goes to the encounter of previous studies that showed a decrease in survival with the increase of the SYNTAX tertile,[6] which may occur due to the increased anatomic complexity of the lesions in the high SYNTAX score group. The Intermediate score group did not present any significant difference in the occurrence of this outcome comparing to the other two groups in our study.

Despite this difference between the Low and High groups, we found that the patients' SYNTAX score was not an independent predictor for the occurrence of the composite outcome, which was also demonstrated in other studies.[6, 8] Considering this, and according to our results, PCI is a viable option for patients with low SYNTAX scores, and may have worse results in patients with high anatomical complexity lesions. Patients with an Intermediate SYNTAX score may benefit with a case-by-case approach, and PCI could be a good option in selected cases. However, regardless the patients SYNTAX score, a proper discussion in a Heart team meeting should lead to an adequate decision about the revascularization method.

Limitations

In this study we only analyzed patients submitted to PCI procedures for the treatment of LMCA disease. This makes impossible to establish definitive conclusions on the best treatment approach to this disease based only on this analysis, since we do not possess data about CABG procedures and associated outcomes. As such, other studies should be made with this group in consideration.

Also, some of the data concerning the variables in study was not available. This occurred because some of the patients were not followed in CHUC, and it was not possible to

find the information with the means possessed. This may affect the results obtained, and future studies should take in account this factor.

Furthermore, the available sample size was small. This could explain why some known variables with impact in the outcomes of LMCA patients, such as diabetes mellitus, did not reach statistical significance. Therefore, future studies should be designed considering a larger sample size.

Conclusion

In this work, we present the experience with PCI treatment of LMCA disease in CHUC. This disease remains a therapeutic challenge and PCI may be a good treatment alternative in selected groups, especially in patients with low anatomic complexity. In every patient with LMCA disease, but particularly in high SYNTAX score patients and in those with insulin-treated diabetes, atrial fibrillation and valvular heart disease, the adequate revascularization method should be carefully discussed by the Heart team, in order to offer the best possible treatment.

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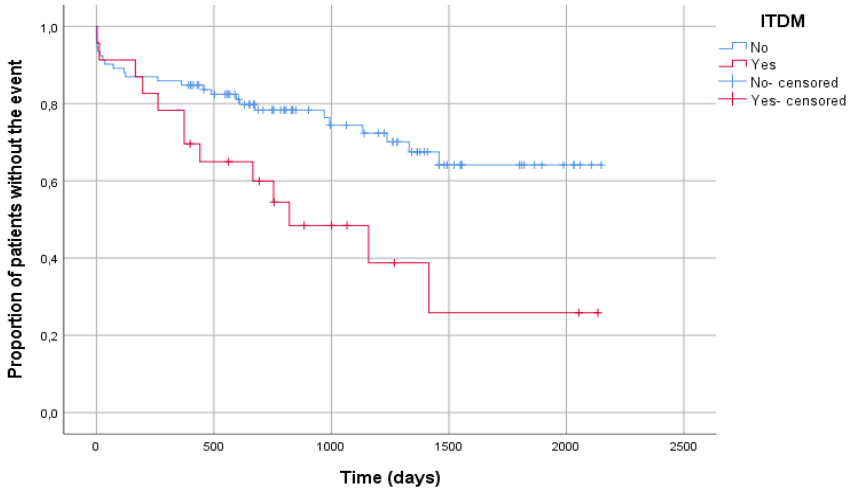
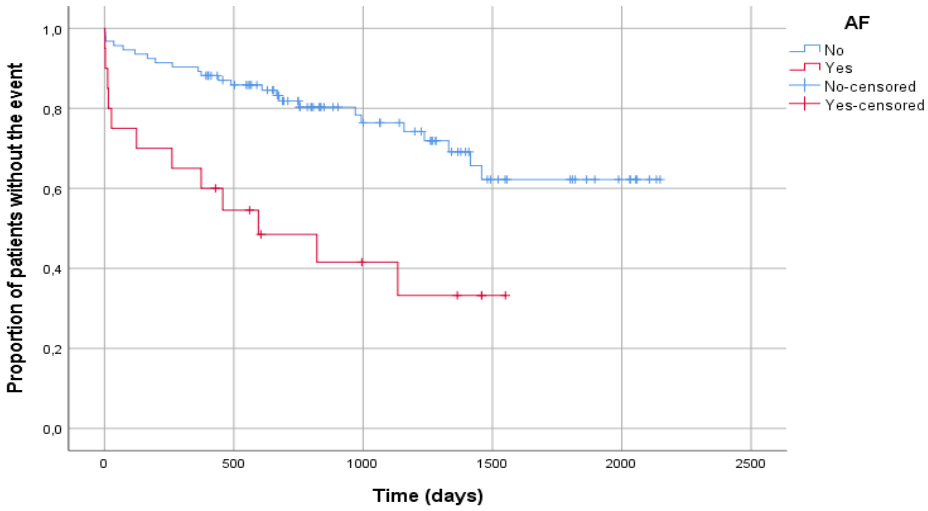
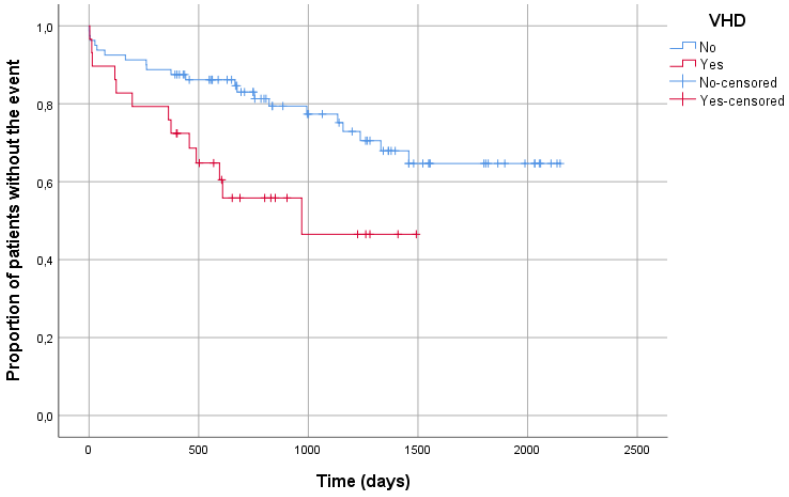
Appendix I – Kaplan-Meier estimate for time to composite endpoint of all-cause mortality and myocardial infarction according to the presence of insulin-treated diabetes mellitus (ITDM).



Appendix II – Kaplan-Meier estimates for time to composite endpoint of all-cause mortality and myocardial infarction according to the presence of atrial fibrillation (AF).



Appendix III – Kaplan-Meier estimates for time to composite endpoint of all-cause mortality and myocardial infarction according to the valvular heart disease (VHD).



Appendix IV- Approval of Ethics Committee of Centro Hospitalar e Universitário de Coimbra

REPÚBLICA PORTUGUESA
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CHUC
CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

Exmº Senhor
Dr. Carlos Santos
Presidente
do Conselho de Administração
Do CHUC

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA Nº: CHUC-163-20	DATA: 23-12-2020

ASSUNTO: Aprovação do Projeto de Investigação CHUC-163-20.

A pedido de Luís Miguel de Sousa Azevedo, recebeu esta Unidade um pedido de autorização de um Projeto de Investigação subordinado ao tema: **«Resultados de um Programa de Tratamento Percutâneo de Lesões do Tronco Comum»**, que colheu parecer favorável da Comissão de Ética deste Centro Hospitalar.

Informa-se V. Exª que este projeto não acarreta qualquer encargo financeiro adicional para o CHUC.

Solicita-se, assim, a autorização do Conselho de Administração para este Projeto.

Com os melhores cumprimentos,

C.H.U.C. - EPE - Conselho de Administração
Autorizado
07.01.2021

Pel'O Centro de Ensaios Clínicos

(Prof. Doutor Ricardo Vieira)

C.H.U.C. - EPE
CONSELHO DE ADMINISTRAÇÃO
Reg. Nº 43 PCA
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Data 4 / 1 / 2021

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CHUC CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

Comissão de Ética para a Saúde

Visto/ A U.I.D.
para difusão
18/12/2020

Dr. Nuno Deveza
Diretor Clínico
C.H.U.C. - EPE

Exmo. Senhor
Dr. Nuno Deveza
Digmº Diretor Clínico do CHUC

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
		Nº 299/CES	17-12-2020

Proc. Nº **CHUC-163-20**

Estudo Observacional: retrospetivo **"Resultados de um programa de tratamento percutâneo de lesões do tronco comum"**
Entrada na UID:02-11-2020
Entrada na CES: 09-11-2020
Visto na Reunião de: 18-11-2020 (**Parecer Desfavorável, Of. 274/20)**
Reentrada na CES: 11-12-2020
Investigador/a/es: Luís Miguel de Sousa Azevedo, Aluno do Mestrado Integrado em Medicina **Coordenador**: Luís Pedro Candal Leite, Médico Assistente Hospitalar em Cardiologia, Assistente Convidado da FMUC **Co-Investigador/a/es**: Lino Manuel Martins Gonçalves, Diretor do Serviço de Cardiologia, Prof Catedrático de Cardiologia da FMUC; Gustavo Manuel de Oliveira Campos, Médico Interno de Formação Específica de Cardiologia
Promotor: Faculdade de Medicina da Universidade de Coimbra
Serviço de Realização: Cardiologia CHUC

Cumpre informar Vossa Ex.ª que a CES - Comissão de Ética para a Saúde do Centro Hospitalar e Universitário de Coimbra, reunida em 16 de dezembro de 2020, após reapreciação do projeto de investigação supra identificado, emitiu o seguinte parecer:

"Esclarecimentos aceites. A Comissão considera que se encontram respeitados os requisitos éticos adequados à realização do estudo pelo que emite parecer favorável ao seu desenvolvimento no CHUC".

Mais se informa que a CES do CHUC deverá ser semestralmente atualizada em relação ao desenvolvimento dos estudos favoravelmente analisados e informada da data da conclusão dos mesmos, com envio de relatório final.

Com os melhores cumprimentos,

A Comissão de Ética para a Saúde do CHUC, E.P.E.

Prof. Doutor João Pedroso de Lima
Presidente

CES do CHUC: Prof. Doutor João Pedroso de Lima, Prof. Doutora Margarida Silvestre, Enfª Adélio Tinoco Mendes, Dra. Cláudia Santos, Dra. Isabel Gomes, Dra. Isabel Ventura, Rev. Pe. Doutor Nuno dos Santos, Dr. Pedro Lopes, Dra. Teresa Monteiro

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