

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL

PhD THESIS
ABSTRACT

LEFT MAIN CORONARY ARTERY
DISEASE - INTERVENTIONAL
REVASCULARIZATION VERSUS
SURGICAL REVASCULARIZATION

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Key words: left main coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, SYNTAX score tertiles

Introduction

Left main coronary artery disease (LMCA) was first described by James Herrick in 1912 in a patient who died from a cardiogenic shock secondary to acute myocardial infarction [1, 2]. Patients presenting a left main coronary artery disease are at high risk because the involvement of this coronary artery segment affects at least 75% of the total flow of the left ventricle, thus leading to a reserved prognosis for the increased risk of massive infarction and sudden cardiac death. Therefore, screening for angiographic exploration of such a lesion is indicative of revascularization regardless the clinical context. Revascularization methods are PCI (percutaneous coronary intervention) or CABG (aorto-coronary bypass).

In this study, we performed a comparative evaluation of patients with LMCAD of the left coronary artery treated by coronary angioplasty and stent implant versus surgical treatment by aorto-coronary bypass. In other words, we aimed to compare the efficacy of PCI treatment versus CABG treatment in patients with significant left main coronary artery disease (LMCAD).

According to the structure imposed by a doctoral study, the thesis comprises two parts: the General Part (Knowledge Stage), dedicated to the most recent theoretical notions adjacent to the research topic and the Special Part (Own Contributions), reserved for own contributions.

The General Part comprises 6 chapters from page 1 to page 31. The first one, entitled "Epidemiology of the left coronary artery trunk disease", presents briefly data on the epidemiology of this type of disease. The next chapter, "Anatomy and physiology of coronary circulation" systematically presents current data on the morphological and functional particularities of this subdivision of the circulatory system. The following three chapters deal with aspects related to the pathophysiology of the left main coronary artery disease, methods for its diagnosis, the main types of revascularization (interventional by PCI and surgical by CABG), but also the drug therapy after revascularization, secondary prevention methods and follow-up strategies. with this disease.

The special part of the paper (own contributions) represents more than two thirds of the content of my doctoral thesis. Within this part, I presented at large an original study conducted over a period of about 7 years in three major university medical centers in Romania: Craiova, Timișoara and Cluj-Napoca. A prospective observational analytical study was conducted and it included 83 patients diagnosed with stenosis of common left main coronary artery and treated either by PCI or by CABG, thus creating two study groups. Depending on the endpoint pursued, other study subgroups were established. When included in the study, all patients were evaluated according to a standard protocol consisting of anamnesis, clinical examination, fasting electrocardiogram, fasting echocardiography and usual and specific biological samples (depending on the symptomatology at presentation). The primary endpoint of my study was mortality from any cause of LMCAD patients treated with either PCI or CABG. Other main endpoints evaluated for this PhD thesis were the symptoms of ischemic heart disease manifested by angina, the need for repeat myocardial revascularization, nonprocedural nonfatal myocardial infarction and reduced ejection fraction of the left ventricle.

First part. The state of knowledge

This lesion (LMCAD) is found in 3 to 5% of patients evaluated by coronary angiography and is frequently accompanied by the concomitant involvement of one or more epicardial coronary vessels [3]. Significant isolated lesion, in the absence of other significant angiographic lesions, is very rare [2].

Although coronary angiography represents the gold standard in the diagnosis and quantification of left main coronary artery stenosis, necropsy studies have shown that stenosis severity is often underestimated in angiographic evaluation [2–4].

LMCAD is an important condition both due to the lack of specific clinical signs at presentation, which often causes an underestimation of its severity, but, above all, due to the increased mortality and morbidity caused by it [2]. The severity of the stenosis may be of prognostic importance.

Myocardial revascularization surgical techniques have evolved with the development of pumps and other procedures, intraoperative ultrasonography, graft selection for total arterial revascularization, intraoperative graft evaluation and minimally invasive procedures.

The current surgical practice has as main purpose the by-pass of all epicardial vessels having a diameter greater than or equal to 1.5 mm and having a lumen reduction greater than or equal to 50%, at least in one image angiography. This is based on the anatomical configuration of complete revascularization [5]. Following the aorto-coronary bypass procedure, in patients with incomplete revascularization, similar [5] or inferior [1] evolutionary results were noted, in contrast to those with complete revascularization.

On the other hand, contemporary PCI standards for left coronary artery disease include imaging procedure and functional evaluation, procedural planning based on clinical and anatomical features with the use of new generation DES, with thin layers of biocompatible and biocompatible polyme, stenting with proximal optimization, post-procedural imaging and functional evaluation with subsequent optimization of double antiplatelet therapy [1].

Second Part. Own cotributions.

Aim and objectives

In this study, we performed a comparative evaluation of patients with common stenosis of the left main coronary artery treated by stent implant coronary angioplasty versus surgical treatment by aorto-coronary bypass. In other words, we aimed to compare the efficacy of PCI treatment versus CABG treatment in patients with significant left ain coronary artery disease (LMCAD).

This study was conducted prospectively and, in order to achieve the main purpose described above, we have established the following objectives:

- ✓ Outline the clinical-pathological characteristics of the patients included in the study;
- ✓ Identification of the risk factors that influenced the evolution of patients with LMCAD treated by the revascularization methods mentioned above;
- ✓ Quantifying the death rate regardless the cause that caused it;
- ✓ Evaluation of the recurrence of the symptoms manifested by angina in the case of revascularized patients;
- ✓ Assessment of the need for myocardial revascularization after previously treated patients with PCI or CABG;
- ✓ Determination of the rate of non-fatal myocardial infarction after revascularization therapy;
- ✓ Quantification of the ejection fraction of the left ventricle and its evaluation to identify the patients included in the study for whom the ejection fraction decreased after applying the therapeutic method of revascularization;

- ✓ Analysis of biological samples;
- ✓ Identification of the prognostic factors for the main objective specified above.

Material and methods

So, we conducted both a transversal and a longitudinal study, a prospective, analytical, descriptive observational study, with a enrollment period from October 2012 to October 2015 and a follow-up period of approximately 3 years for each patient included in the study.

Inclusion criteria:

- acute myocardial infarction without ST segment elevation;
- unstable or stable angina pectoris;
- the presence of stenosis of the left main coronary artery defined as a reduction of more than 50% of the lumen diameter at coronary angiography;
- patients aged over 18 years;
- patient consent to participate in the study.

Exclusion criteria:

- patients who refused myocardial revascularization treatment;
- life expectancy under one year, increased surgical risk determined by Euroscore of at least 8 or higher;
- acute myocardial infarction with ST-segment elevation within the first 24 hours after onset;
- patients who had absolute contraindications to dual antiplatelet therapy;
- patients who refused to participate in the study.

The primary endpoint of our study was all-cause mortality of patients with LMCAD treated with either PCI or CABG. Other main endpoints evaluated in our study were the symptoms of ischemic heart disease manifested by angina, the need for myocardial revascularization, nonprocedural non-fatal myocardial infarction, and reduction of ejection fraction of the left ventricle.

The risk factors according to which the evolution of the patients in our study was monitored were represented by diabetes mellitus, smoking, age and sex..

For statistical analysis all data were initially processed in Microsoft Office Excel 2016 software (Microsoft Corporation, Redmond, Washington, USA) and, after graphical representation, were analyzed using Graph Pad software (version 6 or newer, 6, GraphPad Software , La Jolla, CA, USA), where, first, the mean and standard deviation were calculated for each group variable, then statistical analysis continued. We used the “t Student” test, to evaluate the statistical differences between the averages of two data groups collected from the patients included in the study and the ANOVA variance test to analyze the statistical differences between the averages of more than two data groups. To perform the correlation between the different categories of data, we would use the Pearson correlation test. To analyze whether there is a link between a variable and survival time, we used the Logrank test. In all the cases in which we calculated the value $P < 0.05$, we considered that there is a statistically significant difference between the compared averages from the different groups.

Results

Clinico-pathological features

The clinical-pathological characteristics of the patients included in our study are shown in the following table.

Clinical and pathological features	PCI (n=38, 46%)	CABG (n=45, 54%)	P value
Age (years)	64.32±6.51	63.14±6.21	0.370 [#]
Gender			0.003*
Female	n= 24, (63.14%)	n= 14, (32%)	
Male	n= 14, (36.84%)	n= 31, (68%)	
Body-mass index >30 kg/m ²	29.1±5.2	28.3±4.6	0.640 [#]
Active smoking	n= 28, (75%)	n= 30, (66%)	0.324*
Diabetes mellitus	n= 19, (50%)	n= 17, (38%)	0.270*
Hypertension	n= 28, (73%)	n= 35, (78%)	0.429*
Hypercholesterolaemia	n= 33, (87%)	n= 40, (89%)	0.387*
Left-ventricular ejection fraction	56±5%	57±4%	0.870 [#]
Indication			0.461
Stable angina pectoris	n= 30, (78%)	n= 37, (83%)	
Acute coronary syndrome	n= 8, (22%)	n= 8, (17%)	
EuroSCORE	2.9±2.4	3.4±2.1	0.670 [#]
SYNTAX score	27.53±5.80	30.06±5.33	0.044 [#]
0-22	n= 10, (26%)	n= 7, (16%)	
23-32	n= 19, (50%)	n= 18, (40%)	
≥33	n= 9, (24%)	n= 20, (44%)	
Involved location			0.255*
Ostium and/or mid-shaft	n= 18, (47%)	n= 17, (38%)	
Distal bifurcation	n= 20, (53%)	n= 28, (62%)	

*EuroSCORE = European System for Cardiac Operative Risk Evaluation. SYNTAX= Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. CABG = coronary artery bypass grafting. PCI = percutaneous coronary intervention. Data are reported as mean ± SD for continuous variables and absolute numbers (%) for dichotomous variables. # t test. * Chi-square test with Yates' correction.*

Interventional revascularization versus surgical revascularization

Regarding all-cause mortality of patients with left main coronary artery stenosis (LMCAD), comparing treatment with percutaneous coronary angioplasty (PCI) and treatment with aorto-coronary bypass (CABG), we observed overall mortality of about 23.86% in patients treated with PCI versus 4.54% in patients treated with CABG.

Comparing the onset of the symptoms of ischemic heart disease manifested by angina, in patients with left main coronary artery disease (LMCAD), treated either by percutaneous coronary angioplasty (PCI) or by aorto-coronary bypass (CABG), we have observed an increased rate of angina pectoris recurrence in patients treated with PCI, whereas in patients treated with CABG the rate of angina pectoris recurrence was lower.

Assessing the occurrence of non-fatal acute myocardial infarction in the two groups of patients (PCI vs. CABG) with left main coronary artery disease (LMCAD), we observed an increase in the rate of non-fatal acute myocardial infarction in patients with Percutaneous coronary angioplasty (PCI) is much higher than in patients treated with CABG who had very low rates of non-fatal acute myocardial infarction.

Regarding the need for revascularization after the treatment procedure (PCI vs CABG) in patients with left main coronary artery disease (LMCAD), there was a higher need for patients with percutaneous coronary angioplasty (PCI) compared with the treatment through CABG.

Assessing the left ventricular ejection fraction in patients with left main coronary artery disease (LMCAD) for 3 years, we observed a reduction in patients with percutaneous coronary angioplasty (PCI) compared to patients treated by CABG.

Impact of risk factors on the patients included in the study

Analyzing the mortality of any cause according to the risk factors in patients with left main coronary artery disease, we observed a higher mortality in the group of active smokers, in the group of patients with diabetes compared to those without diabetes, in the male group compared to the female group, but also in the group of patients older than or equal to 65 years old, compared with the patients whose age was under 65 years but there were statistically significant differences only depending on the presence of diabetes and gender.

Regarding the recurrence of the symptoms of ischemic heart disease manifested by angina, depending on the risk factors, in patients with left main coronary artery disease, we observed an increase in the symptoms in the group of active smokers, in the group of patients with diabetes. in the group of male patients compared to female patients but also in the group of patients older than or equal to 65 years. Thus, regarding the recurrence of the symptoms of ischemic heart disease manifested by angina, depending on the risk factors, in the patients with left main coronary artery disease there were statistically significant differences only according to smoking, diabetes and gender of the patients included in the study.

Regarding the occurrence of non-fatal acute myocardial infarction, depending on the risk factors, in the patients with left main coronary artery disease, statistically significant differences were recorded only according to the presence of diabetes.

Analyzing the decrease of the ejection fraction of the left ventricle, according to the risk factors, in the patients with left main coronary artery disease, statistically significant differences were recorded only according to the presence of diabetes and the gender of the patients.

Results of 3-years follow-up of patients with left coronary artery trunk stenosis according to SYNTAX score

Patients with SYNTAX score 0-22 and 23-32 were predominantly treated with PCI (SYNTAX score 0-22: 26% treated with PCI compared with 16% treated with CABG, and SYNTAX SCORE 23-32: 50% treated with PCI comparatively with 40% treated with CABG) while patients with SYNTAX score ≥ 33 were predominantly treated surgically (44% treated with CABG compared to 24% treated with PCI).

At 3-years follow-up, in the patients with SYNTAX score 0-22, Kaplan-Meier curves showed a cause-and-cause mortality rate of 9.48% for the PCI group versus 0% for the CAGB group (HR PCI vs CABG = indefinite, 95 % CI = undefined, $p = 0.7$). In the SYNTAX 23-32 patient group, the Kaplan-Meier curves estimated a 7.75% all-cause mortality rate for the PCI-treated group at 3-years follow-up versus 0% for the CAGB group (HR PCI vs CABG = indefinite, 95% CI = indefinite, $p = 0.19$). In the patient group with SYNTAX score ≥ 33 , at 3 years follow-

up, the Kaplan-Meier curves showed an all-cause mortality rate of 47.98% for the PCI group versus 7.37% for the CAGB group (HR PCI vs CABG = 8.89, 95% CI = 3.01 - 43.9, p = 0.001).

Regarding the symptomatology, in the group of patients with SYNTAX score 0-22, Kaplan-Meier curves showed a pectoral angina rate of 30% for the PCI group, at 3 years follow-up, versus 0% for the CAGB group (HR PCI vs. CABG = undefined, 95% CI = undefined, p = 0.121). In the group of patients with the SYNTAX score 23-32, the Kaplan-Meier curves showed a pectoral angina rate of 61.89% for the PCI group, at 3 years follow-up, versus 40.58% for the CAGB group (HR PCI vs CABG = 1.77, 95 % CI = 1.07 - 5.51, p = 0.079). In the group of patients with SYNTAX score ≥ 33 , at 3 years follow-up, the angina rate was 74.57% for the PCI group versus 43.00% for the CAGB group (HR PCI vs CABG = 3.55, 95% CI = 2.92-15.4, p <0.000).

Analyzing the occurrence of non-fatal myocardial infarction in patients revascularized for stenosis of the common left coronary artery, at 3 years follow-up, in the group of patients with SYNTAX score 0-22, Kaplan-Meier curves estimated a rate of non-fatal myocardial infarction. 10.00% fatal for PCI group versus 0% for CAGB group (HR PCI vs CABG = indefinite, 95% CI = indefinite, p = 0.402). In the group of patients with SYNTAX score 23-32, the Kaplan-Meier curves estimated a non-fatal myocardial infarction rate of 21.62% for the PCI group at 3-years follow-up, versus 11.11% for the CAGB group (HR PCI vs CABG = 2.84, 95% CI = 0.693 - 11.1, p = 0.094). In the group of patients with SYNTAX score ≥ 33 , at 3 years follow-up, the rate of non-fatal myocardial infarction was 43.98% for the PCI group versus 17.12% for the CAGB group (HR PCI vs CABG = 4.44, 95% CI = 1.83 - 21.2, p = 0.001).

Assessing the reduction of the left ventricular ejection fraction at 3-years follow-up, in the patients with SYNTAX score 0-22, the Kaplan-Meier curves estimated a FEVS reduction rate of 10.00% for the PCI group versus 0% for the CAGB group (HR PCI vs CABG = indefinite, 95% CI = indefinite, p = 0.4028). In the group of patients with SYNTAX score 23-32, the rate of reduction of LVEF was 47.61% for the PCI group, at 3-years follow-up, versus 5.55% for the CAGB group (HR PCI vs CABG = 11.37, 95% CI = 2,374 to 20.90, p = 0.0032). In the group of patients with SYNTAX score ≥ 33 , at 3-years follow-up, the decrease rate of LVEF was 61.59% for the PCI group versus 17.12% for the CAGB group (HR PCI vs CABG = 7,778, 95% CI = 4,351 - 32.05 , p = <0.000).

Comparing the need for repeat myocardial revascularization in patients treated for LMCAD, at 3-years follow-up, in patients with SYNTAX score 0-22, the Kaplan-Meier curves estimated a repetition rate of 10% for PCI versus 0. % for the CAGB group (HR PCI vs CABG = indefinite, 95% CI = indefinite, p = 0.402). In the group of patients with SYNTAX score 23-32, the Kaplan-Meier curves estimated a repetition rate of revascularization of 61.89% for the PCI group, at 3-years follow-up, versus 37.03% for the CAGB group (HR PCI vs CABG = 1.77, 95% CI = 1.02 - 5.25, p = 0.132). In the group of patients with SYNTAX score ≥ 33 , at 3-years follow-up, the recurrence rate was 68.21% for the PCI group versus 31.75% for the CAGB group (HR PCI vs CABG = 4.76, 95% CI = 3.37 to 20.5 , p <0.000).

Discussions

The results of this study are comparative with the results of the clinical trials carried out most of the time simultaneously with the follow-up period of the patients included in our study. Until now, 6 large studies have been published regarding the comparison between percutaneous coronary revascularization versus aorto-coronary bypass in patients with left main coronary artery disease: LE MANS [6], Boudriot et al . [7], PRECOMBATED [8], SYNTAX [9], EXCEL [10] and the NOBEL trial [218]. It should be mentioned, that at the time of the beginning of my doctoral studies, only the first two had been published until then.

Conclusions

The aorto-coronary bypass remains the standard treatment for patients at high risk, presenting complex lesions, while for patients with left main coronary artery disease, at low or intermediate risk, percutaneous coronary intervention by stent implantation remains an alternative that does not present significant risks.

The majority of cardiovascular events that occurred in the evolution of patients with left main coronary artery disease, treated either interventionally or surgically, registered the highest prevalence in the group of patients with diabetes, followed by the smoking patients, the male patients and the elderly patients, these four factors representing negative prognostic factors for this category of patients.

The most recommended tool for assessing the complexity of coronary artery anatomy, if they are affected by the atherosclerotic process, is the SYNTAX score.

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