

Stents Versus Bypass Surgery for Left Main Coronary Artery Disease: 3-Year Clinical Outcomes Depending on SYNTAX Score

SILVIU PAUL TRĂȘCĂ¹, EMILIA VIOLETA GOANȚĂ¹,
GEORGICĂ COSTINEL TÂRTEA^{1,2}, PAULINA-LUCIA CIUREA³

¹Department of Cardiology, Emergency County Hospital of Craiova, Romania

²Department of Physiology, University of Medicine and Pharmacy of Craiova, Romania

³Department of Rheumatology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: The purpose of our study was to compare the 3-year of follow-up clinical outcomes in patients suffering from left main coronary artery disease (LMCAD) treated either by percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG) depending on SYNTAX score tertiles. The primary end point of the study was all-cause mortality for the PCI arm versus CABG arm depending on SYNTAX score tertiles. The secondary end points were the recurrence of angina pectoris following revascularization, the acute nonfatal myocardial infarction, the reduction of the left ventricular ejection fraction or the need for myocardial revascularization. With regard to patients with LMCAD, at low risk (SYNTAX score 0-22) there was no difference in the frequency of end-point occurrence among patients treated by PCI compared to CABG. Also, the tendency to increase end point occurrence in patients with LMCAD treated by PCI compared to patients treated by CABG was more evident in patients at intermediate risk, but the significant statistical difference was recorded only in the occurrence of acute myocardial infarction. Regarding the patients with LMCAD at high risk (SYNTAX score over 33) the endpoint occurrence was significantly increased, statistically significant differences were recorded in all evaluated endpoints. In conclusion, coronary artery bypass grafting remains the standard treatment for high-risk patients with complex lesions, while for patients with LMCAD at low or intermediate risk, percutaneous coronary intervention by stent implantation remains an alternative that does not pose significant risks.

KEYWORDS: SYNTAX score, clinical outcomes, left main coronary artery disease, coronary intervention

Introduction

Impairment of the common trunk of the left coronary artery (identified in approximately 4-9% of the patients evaluated by coronary angiography) predisposes patients to an increased risk of major adverse events because the left ventricle depends on the left coronary artery between 75-100% according to the dominant coronary circulation (left or right) [1].

The diagnosis and the optimal management of the patients suffering from left main coronary artery disease (LMCAD) remain currently incompletely elucidated, being an important source of clinical studies, especially in the decision for the surgical or interventional revascularization [1,2].

Myocardial revascularization is performed with the aim of minimizing residual ischemia but also the risk of death and myocardial infarction as outlined in the Clinical Outcomes trial using the Revascularization and Aggressive Drug Evaluation (COURAGE) [3].

In what the indication for myocardial revascularization of LMCAD is concerned, according to both the ESC (European Society of Cardiology) recommendations and the

ACC/AHA (American College of Cardiology/American Heart Association), it is recommended for patients with luminal reduction $\geq 50\%$ of the left main coronary artery [2,4].

Since the development of the coronary surgical revascularization by Alexis Carrel in 1910, subsequent to the first aortocoronary bypass by using a saphenous vein graft by Rene Favaloro in 1968 and the performance of the first angioplasty coronary arteries in patients with left main coronary artery disease made by Andreas Grüntzig in 1977, revascularization techniques (both surgical and interventional) have greatly improved over the last decades [5].

The revascularization methods of LMCAD by percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) were compared in six major clinical trials published over the past 10 years: LE MANS study (2008), SYNTAX (2010 and 2013), Boudriot et al (2011), PRECOMBAT (2011), EXCEL (2016) and NOBLE (2016) [6-13].

Over the years, numerous risk scores have been proposed in order to guide the selection between PCI or CABG for the type of

myocardial revascularization in patients with LMCAD [5].

The most recent guidelines of myocardial revascularization published in 2018 by the ESC recommend the use of the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) risk score published in 2011 after the publication of the trial results with the same name [2,9-11,14].

The purpose of our study was to compare the 3-year follow-up of clinical outcomes in patients suffering from left main coronary artery disease treated either by percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG) depending on SYNTAX score tertiles.

Material and Methods

We conducted a randomized, observational, multicenter study in which we included 83 patients with LMCAD treated either by PCI or CABG from three centers from Romania; each patient was followed for 3 years after the revascularization procedure.

The three centers where the patients were monitored and/or treated were Timisoara, Craiova and Cluj-Napoca.

The inclusion of patients in the study began in 2012 until 2015, the last patient having follow-up in October 2018.

Our study was discussed and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

Each patient included in our study provided written informed and acceptance consent.

It should be noted that the protocol of our study was designed taking into account the Helsinki and Good Clinical Practice regulations as well as all local regulations, and it was approved by the institutional review board in each center from which patients were included.

The appropriate method for revascularization (CABG or PCI) was selected by a multidisciplinary team, "Heart Team", composed of at least one interventional cardiologist and a cardiac surgeon.

The primary end point of the study was all-cause mortality for the PCI arm versus CABG arm depending on SYNTAX score tertiles.

The secondary end points were recurrence of angina pectoris following revascularization, acute nonfatal myocardial infarction, reduction of the left ventricular ejection fraction or need for myocardial revascularization.

Taking into account the current recommendations, the patients included in our study were divided into three groups according to SYNTAX score tertiles: a low risk category (SYNTAX score <22), an intermediate risk category (SYNTAX score 23-32) and an increased risk category (SYNTAX score \geq 33) [2,9-11,14].

SYNTAX score is calculated by the intersection of several anatomical features: the dominant circulation, the coronary segment involved, the diameter and location of the lesions, the severity of the tortuositities, the length of the lesions, the presence of calcification, the presence of a thrombus, the diffuse or small vessels disease [2,14].

We performed all statistical tests by using Graph Pad software (La Jolla, CA, USA).

Following the assessment of the patients included in the study, we obtained also qualitative data (e.g. the gender of the patients) but most data were quantitative and they were expressed as mean and standard deviation (SD).

We used the "t Student" test to assess the statistical differences between the averages of two data groups and the ANOVA variance test to analyze the statistical differences between the averages of more than two data groups.

Chi square test was also used. For the survival variables we used the median survival time, these variables being represented by the Kaplan-Meier survival curves.

We used the Logrank test to analyze a link between a variable and the survival time, and to quantify the importance of the link between a variable and the survival time, we used the hazard rate (HR) with the associated confidence interval (CI). In all cases where we calculated the p value, $p < 0.05$ was considered a statistically significant difference between the average of the groups that were compared.

Moreover, the value of $p < 0.05$, 0.01 and 0.001 represented a statistically significant difference, a high and very high significant.

Results

Patient baseline and lesion characteristics are described in Table 1.

Of the 83 patients with LMCAD enrolled in our study, 38 (46%) were treated by PCI and 45 (54%) were treated by CABG.

The mean age of the patients was 64.32 ± 6.51 years in the PCI group and 63.14 ± 6.21 in the CABG group.

In the PCI group, women (n=24.64%) predominated compared to men (n=14.36%),

while men (n=31.68%) predominated in the CABG group compared to women (n=14, 32%). In the PCI group a number of 19 patients (50%) had a medically treated diabetes while in the CABG group the percentage was lower (n=17, 38%).

However, in both groups, patients presented a high percentage of hypertension (73% in the PCI group and 78% in the CABG group), hypercholesterolaemia (87% in the PCI group and 89% in the CABG group) and many were

active smokers (75% in the PCI group and 66% in the CABG group).

Patients with SYNTAX score 0-22 and 23-32 were treated predominantly by PCI (SYNTAX score 0-22: 26% treated by PCI versus 16% treated by CABG, and SYNTAX SCORE 23-32: 50% treated by PCI compared to 40% treated by CABG) while patients with SYNTAX score ≥ 30 were predominantly surgically treated (44% treated by CABG versus 24% treated by PCI).

Table 1. Baseline Clinical and Angiographic Characteristics of the Study Groups

Clinical and pathological features	PCI (n=38, 46%)	CABG (n=45, 54%)	P value
Age (years)	64.32 \pm 6.51	63.14 \pm 6.21	0.370 [#]
Gender			0.003*
Female	n=24, (64%)	n=14, (32%)	
Male	n=14, (36%)	n=31, (68%)	
Body-mass index >30 kg/m ²	29.1 \pm 5.2	28.3 \pm 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 \pm 5%	57 \pm 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 \pm 2.4	3.4 \pm 2.1	0.670 [#]
SYNTAX score	27.53 \pm 5.80	30.06 \pm 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%)	
<p><i>Euro SCORE=European System for Cardiac Operative Risk Evaluation.</i> <i>SYNTAX=Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.</i> CABG=coronary artery bypass grafting. <i>PCI=percutaneous coronary intervention. Data are reported as mean\pmSD for continuous variables and absolute numbers (%) for dichotomous variables. # t test.</i> <i>*Chi-square test with Yates' correction</i></p>			

Regarding the involvement of the lesion location (for example the left main coronary artery lesions are shown in Fig.1), 47% of the PCI group had ostium and/or mid-shaft location

and 53% distal bifurcation location while in CABG group 38% had ostium and/or mid-shaft location and 62% distal bifurcation location.

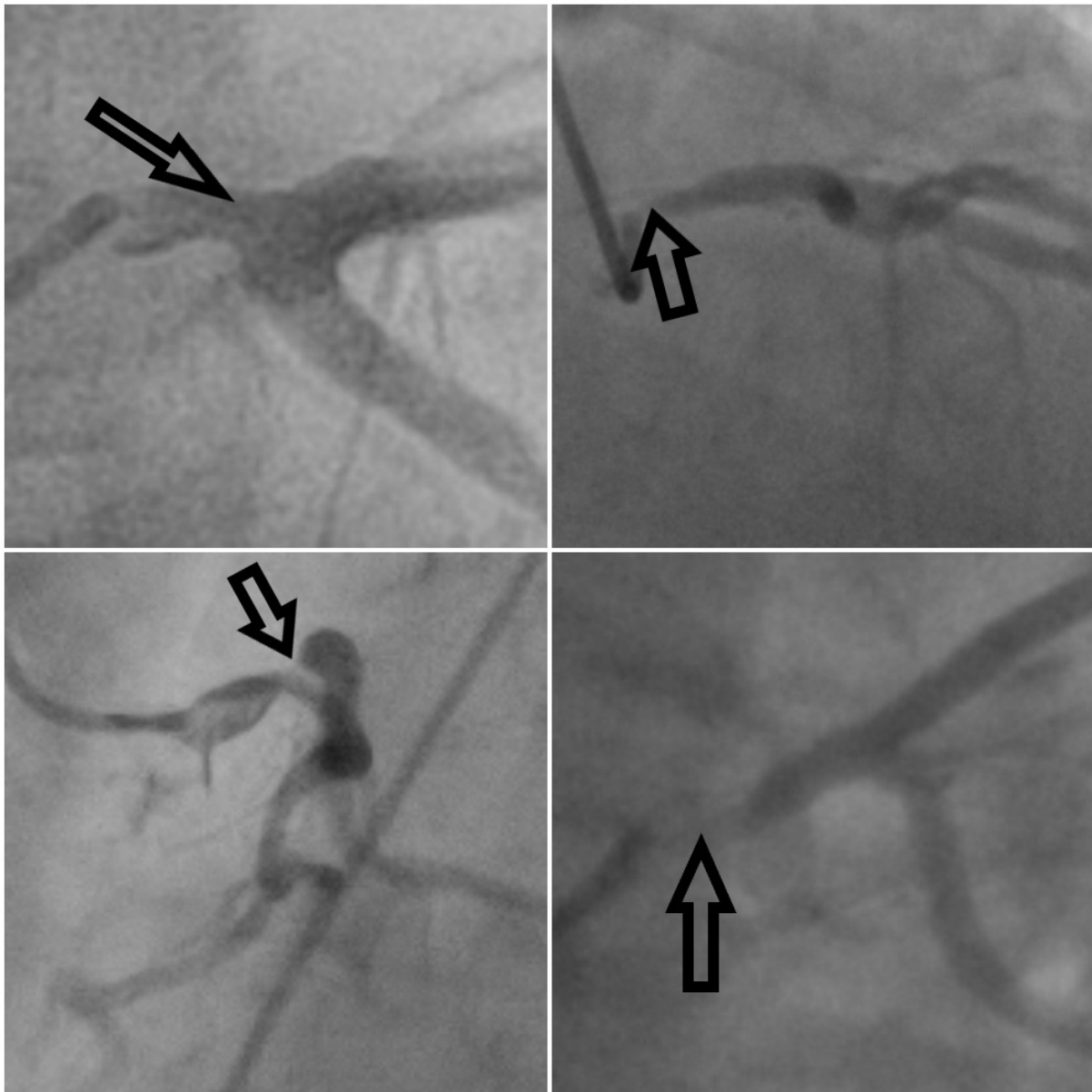


Fig.1. Different findings of the left main coronary artery disease

At 3 years of follow-up, in the SYNTAX score 0-22 group, Kaplan-Meier estimates of all-cause mortality rates were 9.48% for the PCI group versus 0% for the CABG group (HR PCI vs. CABG=undefined, 95% CI=undefined, $p=0.7$) (Fig.2A).

In the SYNTAX score 23-32 group, Kaplan-Meier estimates all cause mortality rates were 7.75% for the PCI group at 3 years of

follow-up versus 0% for the CABG group (HR PCI vs. CABG=undefined, 95% CI=undefined, $p=0.19$) (Fig.2B).

In the SYNTAX score ≥ 33 group, at 3 years of follow-up, all-cause mortality rates were 47.98% for the PCI group versus 7.37% for the CABG group (HR PCI vs. CABG=8.889, 95% CI=3.017 to 43.98, $p=0.0010$) (Fig.2C).

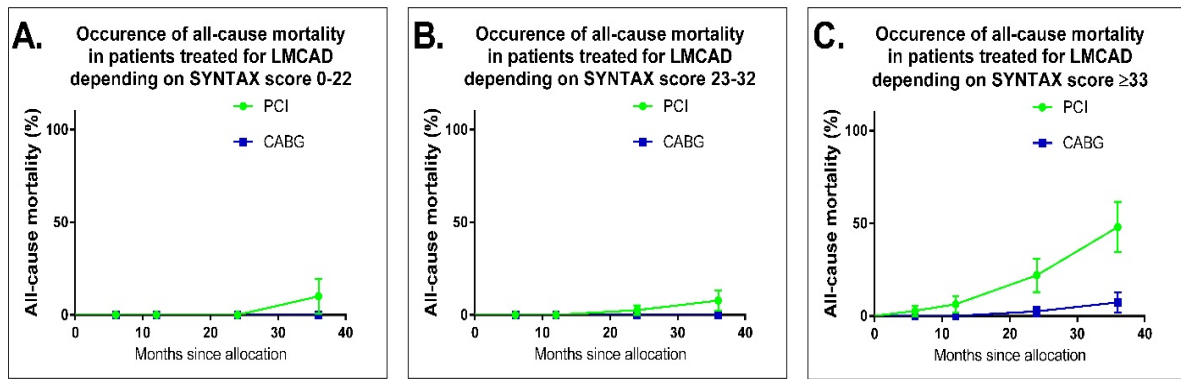


Fig.2. Kaplan-Meier estimates all-cause mortality rates by baseline SYNTAX score tertiles (A-low risk, B-intermediate risk and C-high risk)

Concerning the symptomatology, in the SYNTAX score 0-22 group, Kaplan-Meier estimates angina pectoris rates were 30% for the PCI group at 3 years of follow-up versus 0% for the CABG group (HR PCI vs. CABG=undefined, 95% CI=undefined, p=0.1213) (Fig.3A).

In the SYNTAX score 23-32 group, Kaplan-Meier estimates of angina pectoris rates

were 61.89% for the PCI group at 3 years of follow-up versus 40.58% for the CABG group (HR PCI vs. CABG=1.776, 95% CI=1.076 to 5.519, p=0.0790) (Fig.3B).

In the SYNTAX score ≥33 group, at 3 years of follow-up, angina pectoris rates were 74.57% for the PCI group versus 43.00% for the CABG group (HR PCI vs. CABG=3.556, 95% CI=2.925 to 15.41, p <0.0001) (Fig.3C).

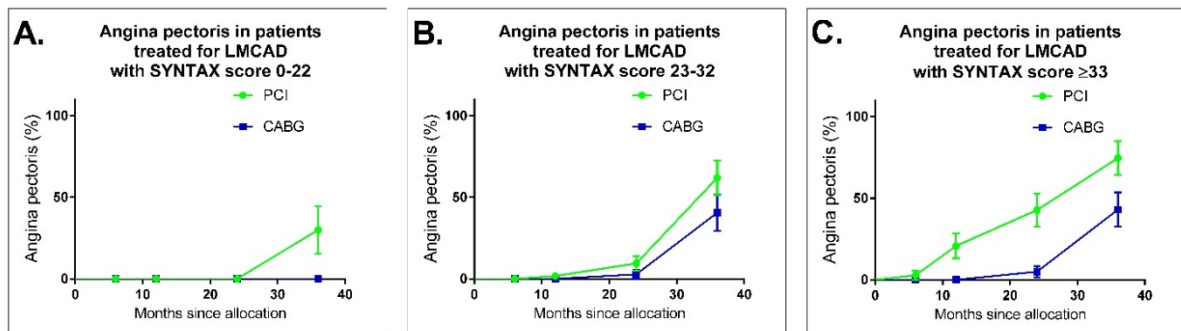


Fig.3. Kaplan-Meier estimates angina pectoris rates by baseline SYNTAX score tertiles (A-low risk, B-intermediate risk and C-high risk)

Analyzing the occurrence of nonfatal myocardial infarction in patients treated for LMCAD, at 3 years of follow-up, in the SYNTAX score 0-22 group, Kaplan-Meier estimates nonfatal myocardial infarction rates were 10.00% for the PCI group versus 0% for the CABG group (HR PCI vs. CABG=undefined, 95% CI=undefined, p=0.4028) (Fig.4A).

In the SYNTAX score 23-32 group, Kaplan-Meier estimates of nonfatal myocardial

infarction rates were 21.62% for the PCI group at 3 years of follow-up versus 11.11% for the CABG group (HR PCI vs. CABG=2.842, 95% CI=0.6939 to 11.11, p=0.0964) (Fig.4B).

In the SYNTAX score ≥33 group, at 3 years of follow-up, nonfatal myocardial infarction rates were 43.98% for the PCI group versus 17.12% for the CABG group (HR PCI vs. CABG=4.444, 95% CI=1.837 to 21.20, p=0.0013) (Fig.4C).

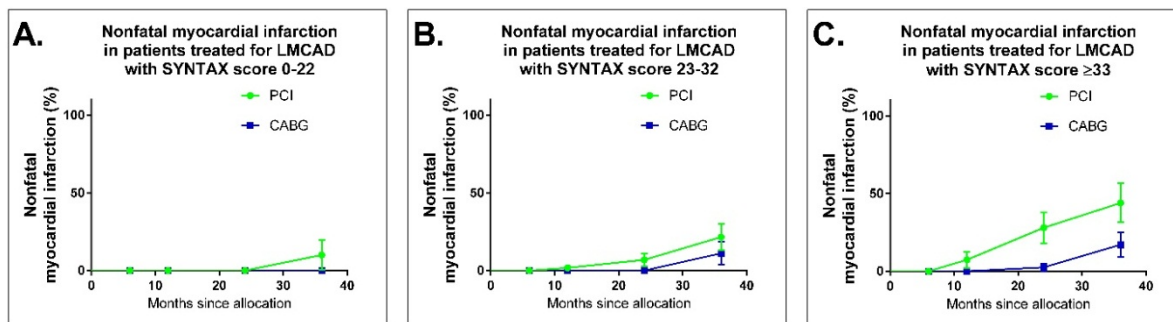


Fig.4. Kaplan-Meier estimates nonfatal myocardial infarction by baseline SYNTAX score tertiles (A-low risk, B-intermediate risk and C-high risk)

Assessing the reduction of the left ventricular ejection fraction at 3 years of follow-up, in the SYNTAX score 0-22 group, Kaplan-Meier estimates the left ventricular ejection fraction reduced rates were 10.00% for the PCI group versus 0% for the CABG group HR PCI vs. CABG=undefined, 95% CI=undefined, p=0.4028) (Fig.5A).

In the SYNTAX score 23-32 group, the Kaplan-Meier estimates of the left ventricular ejection fraction reduced rates were 47.61% for

the PCI group at 3 years of follow-up versus 5.55% for the CABG group (HR PCI vs. CABG=11.37, 95% CI=2.374 to 20.90, p=0.0032) (Fig.5B).

In the SYNTAX score ≥ 33 group, at 3 years of follow-up, the left ventricular ejection fraction reduced rates were 61.59% for the PCI group versus 17.12% for the CABG group (HR PCI vs. CABG=7.778, 95% CI=4.351 to 32.05, p=0.0001) (Fig.5C).

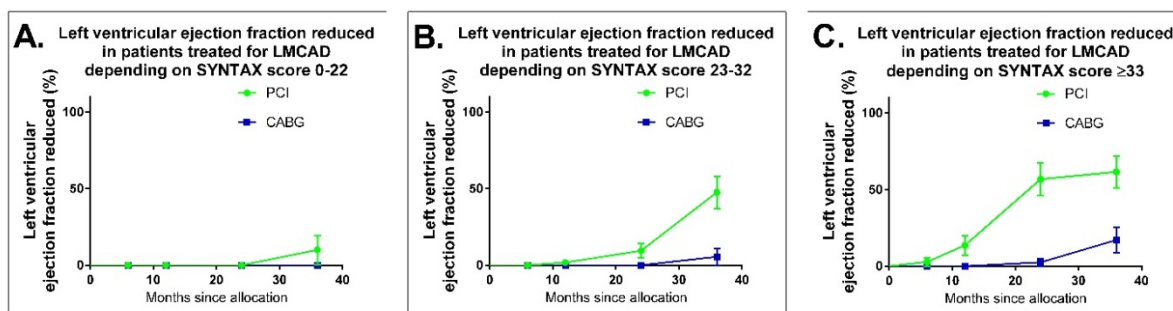


Fig.5. Kaplan-Meier estimates left ventricular ejection fraction reduced by baseline SYNTAX score tertiles (A-low risk, B-intermediate risk and C-high risk)

Comparing the need to repeat myocardial revascularization in patients treated for LMCAD, at 3 years of follow-up, in the SYNTAX score 0-22 group, Kaplan-Meier estimates that the revascularization rates were 10% for the PCI group versus 0% for the CABG group (HR PCI vs. CABG=undefined, 95% CI=undefined, p=0.4028) (Fig.6A).

In the SYNTAX score 23-32 group, the Kaplan-Meier estimates that repeat

revascularization rates were 61.89% for the PCI group at 3 years of follow-up versus 37.03% for the CABG group (HR PCI vs. CABG=1.776, 95% CI=1.024 to 5.255, p=0.1325) (Fig.6B).

In the SYNTAX score ≥ 33 group, at 3 years of follow-up, repeat revascularization rates were 68.21% for the PCI group versus 31.75% for the CABG group (HR PCI vs. CABG=4.762, 95% CI=3.370 to 20.52, p<0.0001) (Fig.6C).

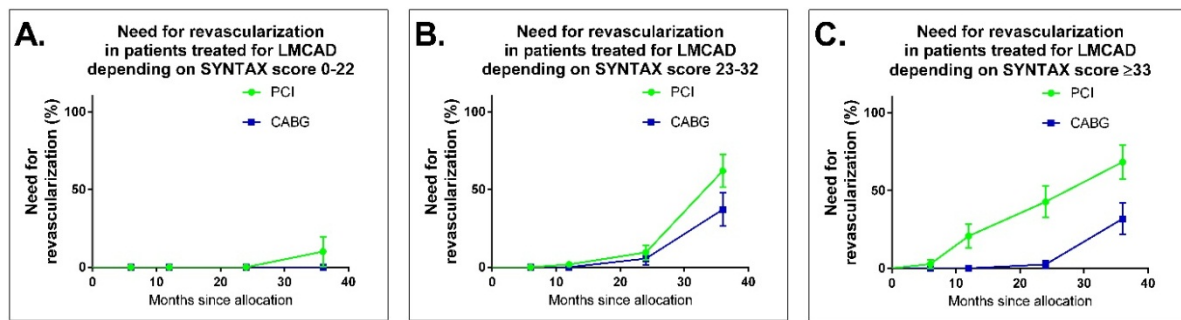


Fig.6. Kaplan-Meier estimates repeat revascularization reduced by baseline SYNTAX score tertiles (A-low risk, B-intermediate risk and C-high risk)

Discussions

Over the years several risk scores were proposed to guide the decision on the type of revascularization (percutaneous coronary intervention by stents-PCI or coronary artery bypass grafting (CABG) in patients with left main coronary artery disease, depending on the anatomical and/or clinical features [5].

The most accepted score pattern was the SYNTAX score, with the new version SYNTAX score II, which besides the anatomical characteristics (dominant coronary circulation, coronary segment involved, lesion diameter and location, severity of tortuosities, lesion length, presence of calcification, thrombus present, diffuse or small vessels disease) also takes into account clinical features (gender, age, serum creatinine clearance, chronic obstructive pulmonary disease, presence of left main coronary artery disease or left ventricular ejection fraction) [1,9-11,14].

In our study, based on SYNTAX score, both primary endpoint and secondary endpoint were higher in patients treated by PCI than in patients treated by CABG, regardless the risk classes.

With regard to patients with LMCAD, at low risk (SYNTAX score 0-22) there was no difference in the frequency of end-point occurrence among patients treated by PCI compared to CABG.

Also, the tendency to increase end point occurrence in patients with LMCAD treated by PCI compared to patients treated by CABG was more evident in patients at intermediate risk, but the significant statistical difference was recorded only in the occurrence of acute myocardial infarction.

Regarding the patients with LMCAD at high risk (SYNTAX score over 33) the endpoint occurrence was significantly increased, statistically significant differences were

recorded in all evaluated endpoints. It should be specified that the methods of revascularization (percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG)) in patients with LMCAD were compared in six major clinical trials published over the past 10 years: LE MANS study (2008), SYNTAX (2010 and 2013), Boudriot et al (2011), PRECOMBAT (2011), EXCEL (2016) and NOBLE (2016) [6-13].

Also we previously published a study in which we analyzed the major adverse cardiac and cerebrovascular events (MACCE) in PCI-treated LMCAD patients compared to patients treated by CABG, revealing higher rates of MACCE in patients treated by PCI [15].

The first study to compare PCI versus CABG treatment in patients with LMCAD was the Study of Unprotected Left Main Stenting Versus Bypass Surgery (LE MANS), conducted between 2001 and 2004, which followed the left ventricular ejection fraction, highlighting the superiority of PCI versus CABG, but the main limitation of this study was the small number of patients included (105) [6].

The next study comparing these two patient groups was the German trial which included 210 patients unlike LE MANS included major adverse cardiac and cerebrovascular events (MACCE), highlighting significant differences in the need for revascularization, this being larger in the PCI group [7].

Another study that randomized 600 patients with LMCAD treated either by PCI or CABG was conducted in the South Korean population, indicating an increased recurrence rate of myocardial ischaemia, but this study was not fully able to compare the rates of occurrence of other MACCEs due to their low incidence [8].

In the SYNTAX trial involving 1,800 patients, the mortality rate was approximately equal in the two compared groups, while the

stroke rate was higher in the CABG group and the revascularization rate was higher in the PCI group [9-11].

The last two large trials, which took place in similar periods and included a similar number of patients, EXCEL and NOBLE, both published in 2016, also had significant differences between them. If the need for revascularization was greater in the PCI group, in both trials, in EXCEL death, stroke or myocardial infarction were the same in both groups, while, at this point, NOBLE presented the superiority of CABG versus PCI [12,13].

Conclusion

In conclusion, coronary artery bypass grafting remains the standard treatment for high-risk patients with complex lesions, while for patients with LMCAD at low or intermediate risk, percutaneous coronary intervention by stent implantation remains an alternative that does not have significant risks.

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*Corresponding Author: Georgică Costinel Târtea, Department of Physiology,
University of Medicine and Pharmacy of Craiova, Petru Rareș Street 2, 200349 Craiova, Romania,
e-mail: georgetartea@gmail.com*