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The impact of left circumflex coronary artery ostium stenosis on outcomes of patients after percutaneous coronary intervention for unprotected left main disease

Short title: The impact of LCX ostium stenosis on unprotected LM PCI

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WHAT'S NEW?

The impact of left circumflex coronary artery (LCX) ostium atherosclerosis in left main coronary artery (LM) bifurcation disease is not well-known. This study aimed to evaluate whether the involvement of LCX ostium significantly influence the results of patients undergoing unprotected LM percutaneous coronary intervention (PCI). The main finding is that the LCX ostium involvement in LM disease PCI is not associated with adverse long-term mortality, which is highly beneficial for the Heart Team decision making process. There is no significant difference in long-term mortality between the groups with one-stent or two-stent techniques in patients with LM disease and LCX ostium stenosis. No significant differences in long-term mortality were observed, regardless of the presence of coexisting lesions in the LCX ostium or left anterior descending artery ostium. Subgroup of patients without significant LCX

ostium disease who underwent LCX stenting during LM PCI, because of the plaque burden shift or carina shift, presents favorable long-term outcomes.

ABSTRACT

Background: The impact of left circumflex coronary artery (LCX) ostium atherosclerosis in left main coronary artery (LM) bifurcation disease is not well-known.

Aim: The aim of the study was to assess whether the involvement of LCX ostium carries prognostic implications in patients undergoing unprotected LM percutaneous coronary intervention (PCI).

Methods: Consecutive 564 patients with unprotected LM (ULMCA) disease who underwent LM PCI between January 2015 and February 2021, with at least 1-year available follow-up were included in the study. First group composed of 145 patients with ULMCA disease with LCX ostium stenosis and the second group consisted of 419 patients with ULMCA disease without LCX ostium stenosis.

Results: Patients in group with ULMCA disease with LCX ostium stenosis were significantly older and comorbidities were found more often in this group. Two stents technique was used more often in group with LCX ostium stenosis (62.8% vs. 14.6%; P <0.001). During 7-year follow-up, all-cause mortality between groups with and without LCX ostium stenosis did not differ significantly (P = 0.50). The use of one-stent or two-stent technique also did not impact the mortality in patients with LCX ostial lesions group (P = 0.75). Long-term mortality subanalysis for three groups of patients: (1) patients with LM + LCX ostium stenosis; (2) LM + left anterior descending artery (LAD) ostium stenosis; (3) LM + LCX ostium + LAD ostium stenosis also did not differ significantly (P = 0.63).

Conclusions: LCX ostium involvement in LM disease PCI is not associated with adverse long-term outcomes, which is highly beneficial for the Heart Team decision making process.

Key words: left circumflex coronary artery ostium, percutaneous coronary intervention, unprotected left main coronary artery

INTRODUCTION

Percutaneous coronary intervention (PCI) in left main coronary artery (LM) disease with documented favorable results in large studies is widely used worldwide. However, the impact of left circumflex coronary artery (LCX) ostium atherosclerosis in LM bifurcation disease is not well-known. Evidence from computed tomography angiography and fractional flow

reserve (FFR) shows that the side branch supplies a smaller portion of the myocardium compared to the main branch and that a stenosis in the side branch is less likely to result in significant ischemia compared to a similar stenosis in the main artery [1]. Nevertheless, side branch occlusion is one of the most significant potential complications after LM stenting and may be a substantial reason why operators choose two-stent technique [2]. Significant ostium stenosis of the side branch has also been reported to be a frequent source of side branch occlusion after stent implantation in the main vessel [3]. The European Bifurcation Club advocates for the use of "jailing wire" technique which involves leaving a wire in the side branch while a stent is implanted in the main branch [4]. The study based on the small group showed that the patients with a higher FFR in jailed LCX had better long-term results than those with a low FFR [5]. In terms of the one-stent technique in LM PCI, two mechanisms of acute luminal loss at the ostium of the left circumflex coronary artery have been suggested, i.e. carina shift and plaque shift [6–8]. Angioplasty in the area of huge atherosclerotic plaque around the bifurcation often results in plaque burden shift to the coronary branch, sometimes causing subsequent occlusion [9]. However, recent articles proved that the carina shift was the principal mechanism of ostial LCX lumen loss during LM PCI [10]. In study performed by Kang et al. carina shift was associated with a narrow distal angle between the LAD and the LCX and a wide proximal angle between the LCX and the LM [10].

In this study, we aimed to assess whether the involvement of LCX ostium carries prognostic implications in patients undergoing unprotected LM PCI.

METHODS

Our study is a part of a larger project concerns LM disease [11–13]. Currently, we analyzed all 564 patients with unprotected LM (ULMCA) disease PCI and with at least 1-year available follow-up. Patients with significant LM stenosis (≥50% diameter) were prospectively enrolled between January 2015 and February 2021 in the study [14]. An ostial LCX lesion was defined as a lesion with at least 50% diameter stenosis by visual assessment and within 3 mm of the left main stem. Patients were divided into two groups: first group composed of 145 patients with unprotected LM disease with LCX ostium stenosis and the second group consisted of 419 patients with unprotected LM disease without LCX ostium stenosis. Established primary outcomes were in-hospital death, in-hospital myocardial infarction (MI), and long-term all-cause death (median [interquartile range (IQR)] follow-up was 1411 (interquartile range: 908, max 2553) days]. Survival analysis data were gathered by telephone contact or with the use of National Health Fund information. IVUS or OCT imaging were used in 202 (35.8%) patients

and were not analyzed in great detail. The antiplatelet regimens were low-dose aspirin (75 mg daily) and clopidogrel (75 mg daily) for a minimum of 6 months after PCI, with the intention of 12 months of dual antiplatelet therapy, in patients without contraindications switch to ticagrelor or prasugrel was allowed.

Statistical analysis

All continuous variables were presented as medians (interquartile range [IQR]). Categorical variables were presented as numbers and percentages and were compared using the test for proportions or Fisher's exact test. The normality of the distribution of variables was assessed using the Shapiro–Wilk test. Differences between continuous variables were evaluated with nonparametric Mann-Whitney test. The survival probability at follow-up was calculated using the Kaplan–Meier method. Log-rank tests were used to compare survival between the different groups. *P* values below 0.05 were considered significant. We used the with STATISTICA 13.7 (StatSoft, Inc., Tulsa, OK, US).

RESULTS

Patients in group with ULMCA disease with LCX ostium stenosis were older (median [IQR], 69.0 [65.0–79.0] years vs. 68.0 [62.0–74.0] years; *P* = 0.002) (Table 1). In this group comorbidities like chronic kidney disease (44.8% vs. 28.6%; *P* <0.001), diabetes (46.9% vs. 36.8%; *P* = 0.03) and previous stroke (13.1% vs. 7.9%; *P* = 0.06) were found more often. Naturally Syntax Score was higher in group with LCX ostium stenosis (28.0 [22.25–34.0] vs. 21 [14.0–28.0]; *P* <0.001), also LM calcifications were found more often in this group (19.3% vs. 11.5%; *P* = 0.02). Number of implanted stents (2.0 [2.0–3.0] vs. 1.0 [1.0–2.0]; *P* < 0.001), total length of stents (46.0 [36.0–64.0] vs. 33.0 [22.0–50.0]; *P* <0.001), radiation time (19.5 [14.0–26.0] vs. 15.0 [11.0–21.0]; *P* <0.001) and radiation dose (1436.5 [969–2151] vs. 1120.5 [706.5–1722.5]; *P* <0.001) were higher in patients with LCX ostium lesions (Table 2). Two stents technique was used more often in group with LCX ostium stenosis (62.8% vs. 14.6%; *P* <0.001). The trend towards more frequent use of Crush techniques was observed in group with LCX ostium involvement. Provisional stenting was performed more often in group without LCX ostial disease. There were no differences between two study groups in terms of periprocedural complications, periprocedural mortality and myocardial infarction type 4a. Patients median (IQR) follow-up was 1411 (908–2553) days. At 7-year follow-up, all-cause mortality between groups with and without LCX ostium stenosis did not differ (*P* = 0.50) (Figure 1). There was no difference in long-term all-cause mortality in patients with LCX ostial

lesions who underwent either one-stent or two-stent technique procedures (P = 0.75) (Figure 2). In our cohort, there were some patients without significant LCX ostium disease who underwent LCX stenting during LM PCI (13.4% of patients from group without LCX ostium involvement), because of the plaque burden shift or carina shift, long-term results of these patients were satisfactory (Figure 3). Subanalysis for three groups of patients: (1) patients with LM + LCX ostium stenosis, (2) LM + LAD ostium stenosis, (3) LM + LCX ostium + LAD ostium stenosis was performed. Long-term mortality rates also did not differ in these groups (P = 0.63) (Figure 4).

DISCUSSION

The choice of stenting strategy in LM PCI is generally determined by the stenosis at the LCX ostium, atherosclerotic lesion length, and/or a tough coronary artery side branch access. These situations generally require initial use of two-stent strategies. Bailout stenting of a diseased coronary side branch can often be more demanding than opting for up-front two-stent strategy. In other LM bifurcation cases a provisional stenting strategy is usually chosen [15]. In a study performed by Park et al. [16] group of patients with true bifurcation lesions had a significantly higher risk of MACE than those with non-true bifurcations (HR 1.39; 95% CI 1.08–1.80; P = 0.01), however, this study was not perform only on LM disease population. Moreover, patients with Medina 1-0-1 had lower risk of cardiac death and MI than other patients with true bifurcation lesions [16]. Nevertheless, LCX is not always last in order of numbers in Medina classification. In subanalysis from the EXCEL trial among 524 patients, both LM major side branches i.e. LAD and LCX had an ostial diameter stenosis ≥50% in 34.7% of cases [17]. Among patients who underwent provisional stenting, a bailout stent was implanted in 28.6% of those with and 12.1% without both side branches ostium stenoses (P = 0.0005) [17]. Bailout stenting was performed in 1 in 6 cases in EXCEL, although it was needed more often when the major coronary side branch, usually the LCX, had ostium stenosis. In EXCEL all-cause mortality rates were insignificantly lower in group with LM bifurcation without involvement of both side branches ostia treated with a provisional approach vs planned two-stent technique (6.1% vs. 13.0%; hazard ratio [HR], 0.46; 95% CI, 0.21–1.01), however, both one- and two-stent techniques in LM disease where both ostial coronary side branches were affected, resulted in comparable mortality rates [17]. In EBC MAIN study patients with true bifurcation left main stem lesions who underwent PCI had fewer major cardiac incidents using the stepwise layered provisional method compared to planned dual stenting, although the difference was not

statistically significant [18]. Therefore, the stepwise provisional approach should continue to be the preferred option for intervention in bifurcation of the distal left main stem [18].

Study limitations

One limitation of the study was the absence of a surgical group for comparison. Nevertheless, examining such a group alongside the CABG group was not within the study's intended scope. Additionally, while the study was based on a prospective registry, not all clinical data was accessible. Thirdly, follow-up did not include analysis of antiplatelet regimen as well as duration of DAPT after discharge. Lastly, intravascular imaging (IVUS or OCT) were not analyzed in great detail.

CONCLUSIONS

In this study we evaluated whether the involvement of LCX ostium significantly influence the results in real-world patients undergoing unprotected LM PCI. As far as we know this is the first study to assess this issue in the broad sense. The main finding of the study is that the LCX ostium involvement in LM disease PCI is not associated with adverse long-term mortality, which is highly beneficial for the Heart Team decision making process. Moreover, there was no significant difference in long-term mortality between the groups with one-stent or two-stent techniques in patients with LM disease and LCX ostium stenosis. Also there were no significant differences in long-term mortality regardless of coexisting LCX ostium or LAD ostium lesions. An interesting subgroup of patients without significant LCX ostium disease who underwent LCX stenting during LM PCI, because of the plaque burden shift or carina shift, also presented good long-term outcomes.

Article information

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Table 1. Study population baseline characteristics

Variable	**Patients with unprotected LM disease with LCX ostium stenosis (n = 145)**	**Patients with unprotected LM disease without LCX ostium stenosis (n = 419)**	***P*-value**
Age, year, median (IQR)	69.0 (65.0–79.0)	68.0 (62.0–74.0)	**0.002**
Sex, female, n (%)	38 (26.2)	104 (24.8)	0.74
Hypertension, n (%)	123 (84.8)	344 (82.1)	0.45
CKD, n (%)	65 (44.8)	120 (28.6)	**<0.001**
DM, n (%)	68 (46.9)	154 (36.8)	**0.03**
Stroke/TIA, n (%)	19 (13.1)	33 (7.9)	0.06
PVD, n (%)	27 (18.6)	61 (14.6)	0.25
AF, n (%)	26 (17.9)	58 (13.8)	0.23
Prior MI, n (%)	68 (46.9)	205 (48.9)	0.67
Stable angina, n (%)	76 (52.4)	239 (57.0)	0.33
Unstable angina, n (%)	35 (24.1)	119 (28.4)	0.32
NSTEMI, n (%)	28 (19.3)	55 (13.1)	0.07
STEMI, n (%)	6 (4.1)	15 (3.6)	0.76
Prior PCI LAD, n (%)	38 (26.2)	98 (23.4)	0.49
Prior PCI LCX, n (%)	27 (18.6)	66 (15.8)	0.42

Prior PCI RCA, n (%)	38 (26.2)	137 (32.7)	0.15
LVEDD, mm, median (IQR)	50.0 (47.0–56.0)	50.0 (46.0–55.0)	0.42
LVEF, %, median (IQR)	50.0 (45.0–60.0)	55.0 (45.0–60.0)	0.18
Coronary artery disease characteristics			
Syntax score, median (IQR)	28.0 (22.25–34.0)	21 (14.0–28.0)	**<0.001**
LM trifurcation, n (%)	23 (15.9)	50 (11.9)	0.22
LM calcificatio n, n (%)	28 (19.3)	48 (11.5)	**0.02**
RCA recessive (a), n (%)	11 (7.6)	32 (7.6)	0.98
RCA with critic al stenosis (b), n (%)	30 (20.7)	56 (13.4)	**0.03**
RCA total occlu sion (c), n (%)	22 (15.2)	66 (15.8)	0.87
Lack of RCA su pport to LMCA D (a+b+c), n (%)	63 (43.4)	154 (36.8)	0.15

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; LAD, left anterior descending; LCx, left circumflex; LM, left main; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIA, transient ischemic attack

Table 2 Left main percutaneous coronary intervention procedure characteristics

Variable	**Patients with unprotected LM disease with LCX ostium stenosis (n = 145)**	**Patients with unprotected LM disease without LCX ostium stenosis (n = 419)**	***P*-value**
Number of stents, median (IQR)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	< **0.001**
Total length of implanted stents, mm, median (IQR)	46.0 (36.0–64.0)	33.0 (22.0–50.0)	< **0.001**
Radiation time, min, median (IQR)	19.5 (14.0–26.0)	15.0 (11.0–21.0)	< **0.001**
Radiation dose, mGy, median (IQR)	1436.5 (969–2151)	1120.5 (706.5–1722.5)	< **0.001**
Contrast volume, ml, median (IQR)	250.0 (200–300)	227.5 (190–300)	0.13
Stenting LM bifurcation, n (%)	145 (100)	363 (86.6)[a]	–
One-stent technique, n (%)	54 (37.2)	310 (85.4)	< **0.001**
Two-stents technique, n (%)	91 (62.8)	53 (14.6)	
Two-stents techniques	n = 91	n = 53	

Crush / DK-Crush, n (%)	56 (61.5)	24 (45.3%)	0.071
Cullote, n (%)	2 (2.2)	0 (0)	
T-stenting, n (%)	17 (18.7)	8 (15.1)	
Provisional stenting, n (%)	16 (17.6)	21 (39.6)	
IVUS/OCT, n (%)	36 (24.8)	166 (39.6)	**0.001**

[a]In this group, the percentages do not add up to 100% because not all patients underwent LM bifurcation percutaneous coronary intervention

Abbreviations: LM, left main, DK-Crush, double kissing crush technique

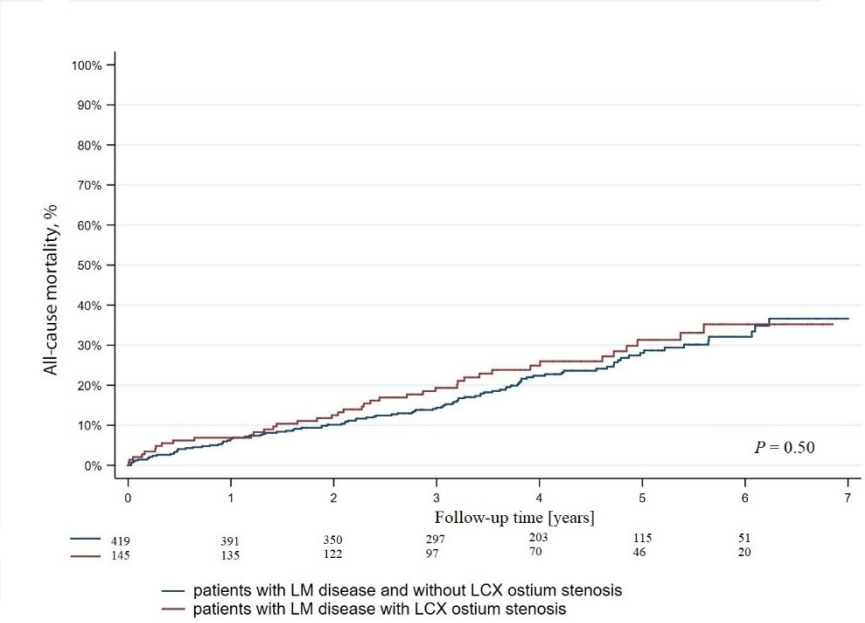

Figure 1. Kaplan-Meier analysis of all-cause mortality: patients with unprotected LM disease with LCX ostium stenosis vs patients with unprotected LM disease without LCX ostium stenosis

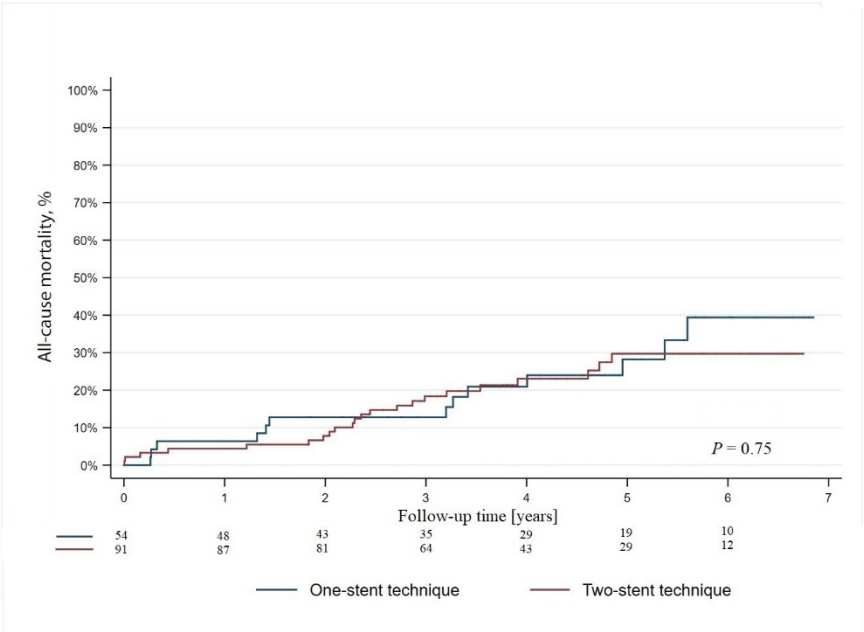

Figure 2. Kaplan-Meier analysis of all-cause mortality: one-stent vs two-stent technique in patients with unprotected LM disease with LCX ostium stenosis

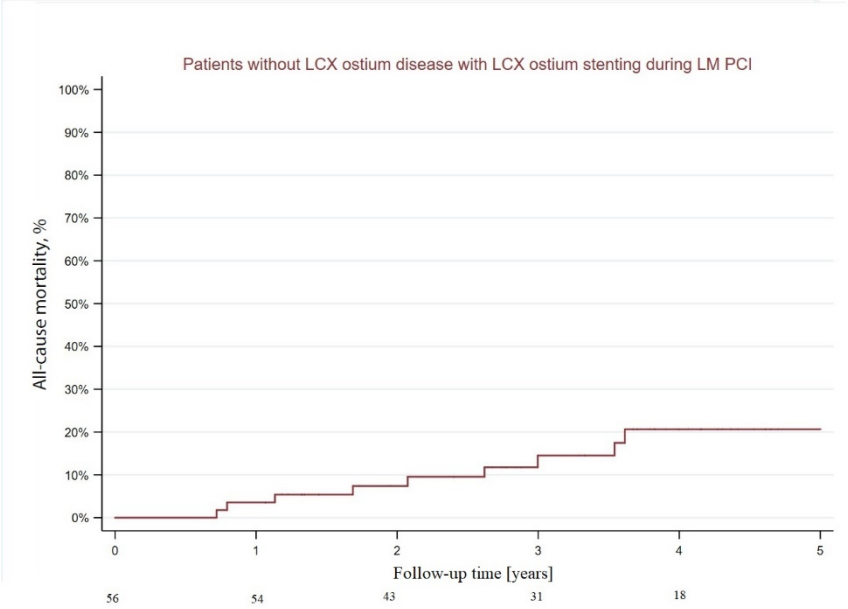

Figure 3. Kaplan-Meier analysis of all-cause mortality: patients without LCX ostium disease with LCX ostium stenting during LM PCI

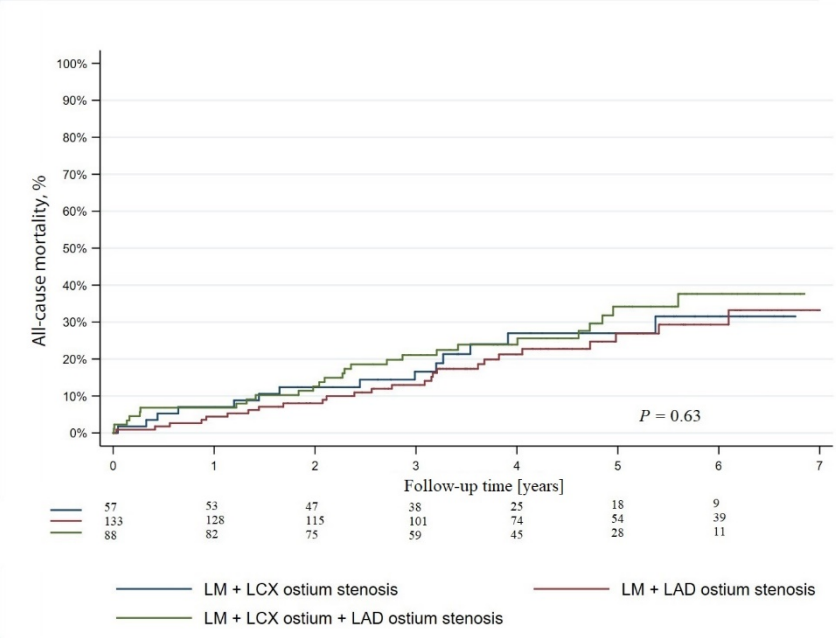

Figure 4. Kaplan-Meier analysis of all-cause mortality: LM+ LCX ostium stenosis vs LM + LAD ostium stenosis vs LM + LCX ostium + LAD ostium stenosis