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Propensity-matched analysis of long-term clinical results after ostial circumflex revascularisation

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ABSTRACT

Background Percutaneous coronary intervention (PCI) of the ostium of the left circumflex artery (LCx) is technically challenging. The aim of this study was to compare long-term clinical outcomes of ostial PCI located in the LCx versus the left anterior descending artery (LAD) in a propensity-matched population.

Methods Consecutive patients with a symptomatic isolated 'de novo' ostial lesion of the LCx or LAD treated with PCI were included. Patients with a stenosis of >40% in the left main (LM) were excluded. A propensity score matching was performed to compare both groups. The primary endpoint was target lesion revascularisation (TLR); other endpoints included target lesion failure and an analysis of the bifurcation angles.

Results From 2004 to 2018, 287 consecutive patients with LAD (n=240) or LCx (n=47) ostial lesions treated with PCI were analysed. After the adjustment, 47 matched pairs were obtained. The mean age was 72±12 years and 82% were male. The LM–LAD angle was significantly wider than the LM–LCx angle (128°±23° vs 108°±24°, p=0.002). At a median follow-up of 5.5 (IQR 1.5–9.3) years, the rate of TLR was significantly higher in the LCx group (15% vs 2%); with an HR of 7.5, 95% CI 2.1 to 26.4, p<0.001. Interestingly, in the LCx group, TLR–LM occurred in 43% of the TLR cases; meanwhile, no TLR–LM involvement was found in the LAD group.

Conclusions Isolated ostial LCx PCI was associated with an increase in the rate of TLR compared with ostial LAD PCI at long-term follow-up. Larger studies evaluating the optimal percutaneous approach at this location are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In-stent restenosis rates following ostial lesions percutaneous coronary intervention are higher and ostial revascularisation shows poorer clinical outcomes compared with non-ostial coronary lesions. Nevertheless, comparison between clinical outcomes after ostial coronary revascularisation according to a specific vessel (left anterior descending artery (LAD) vs left circumflex artery (LCx)) has not yet been performed.

WHAT THIS STUDY ADDS

⇒ Percutaneous treatment of isolated ostial LCx lesions was associated with higher rates of in-stent restenosis compared with ostial LAD revascularisation.

⇒ In the LCx group, the involvement of left main (LM) coronary artery was higher in those cases with target lesion revascularisation.

⇒ There were significant anatomical differences between groups: the angle of the LM and LCx was significantly lower than the angle between LM and LAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results may imply changes in clinical decisions and therapeutic approaches in ostial coronary lesions, leading to use of LM bifurcation techniques with complete lesion coverage as the preferred method.

INTRODUCTION

Ostial coronary lesions constitute a challenge for interventional cardiologists. Previous studies have shown that, in general, ostial lesions present higher rates of in-stent restenosis and poorer clinical outcomes compared with non-ostial coronary lesions.[1–3] Based on these studies, ostial in-stent restenosis rate ranges from 6% to 33% according to types of stent used.[1–3]

One of the factors associated with increased rates of restenosis in ostial lesions is a suboptimal result following percutaneous coronary intervention (PCI). Ostial lesions, due to their proximity to the aortic wall, are more prone to heavy calcification, recoil and rigidity, all of which increase the probability of stent underexpansion.[4 5] In addition, left anterior descending artery (LAD) and left circumflex (LCx) ostial locations are Medina 0,1,0 and 0,0,1 distal left main (LM) bifurcations, which increase the complexity of the treatment due to the proximity of the distal LM.[6]

The optimal percutaneous strategy of ostial LAD or ostial LCx lesions is unknown.[7] Previous studies performed in ostial LAD lesions have shown that placing a stent from the distal LM to the ostium of the LAD (cross-over technique) has better results

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in terms of restenosis and target lesion revascularisation (TLR) compared with ostial stenting[8 9] However, there is a lack of data comparing these two techniques specifically in isolated ostial LCx lesions.

There are data from one study[10] that included patients with distal LM disease that were treated with single-stent cross-over technique from LM to the LAD or LM to LCx. Interestingly, the TLR rates at the LCx ostium were higher, irrespective of LM–LCx or LM–LAD stenting, suggesting that the ostium of the LCx is a unique location that warrants specific studies.

To date, the long-term clinical outcomes of isolated left-sided ostial lesion PCI have not yet been well established. The aim of the study was to assess the long-term clinical outcomes of ostial isolated LCx PCI compared with isolated ostial LAD PCI in a matched population comparison.

METHODS

Study design and population

Demographic, clinical and procedural data were analysed. Patients with ostial lesions in both arteries and those with distal LM involvement of more than 40% (by visual assessment) were excluded. Likewise, patients with prior revascularisation of ostial LCx, ostial LAD or distal LM, as well as those with isolated intermediate ramus ostial stenosis, were not included. Clinical outcomes following ostial LCx and ostial LAD PCI were compared. For this purpose, a matched-pair control group (ostial LAD stenosis) was contrasted with the study group (patients with ostial LCx lesions).

Interventional technique

Coronary angioplasty was performed according to standard protocol and the experience of the operator. Dual antiplatelet treatment with aspirin and clopidogrel was prescribed for at least 1 year in both groups.

Study endpoints and definitions

The LAD was considered the main branch, and the LCx was considered the side branch (SB).

Consequently, all ostial LAD lesions were classified as Medina 0,1,0 and all ostial LCx stenosis were Medina 0,0,1.

All-cause death was defined according to Academic Research Consortium (ARC)- 2 definition.[11] An ostial lesion was defined as a stenosis arising within 3 mm of the vessel origin of the LAD or LCx. A revascularisation was considered ischaemia-driven if it was associated with any of the following: non-invasive positive functional ischaemia study, invasive positive functional ischaemia study (eg, fractional flow reserve), or ischaemic symptoms and an angiographic minimal lumen diameter stenosis of ≥50%.[12] TLR was defined as repeat revascularisation (PCI or bypass graft placement) for restenosis located at the stented segment and/or the 5 mm adjacent to the stent. Target vessel revascularisation (TVR) was defined as repeat revascularisation for a stenosis in another part of the vessel treated at the index PCI (including TLR events).

The primary endpoint of this study was ischaemia-driven TLR at long-term follow-up. The secondary endpoints included all-cause death, cardiac death, myocardial infarction (MI), TVR or freedom from target lesion failure: cardiovascular death, target vessel MI and clinically driven TLR.

Clinical follow-up was performed either telephonically or at the outpatient clinic with a median follow-up time of 5.5 (IQR 1.5–9.3) years.

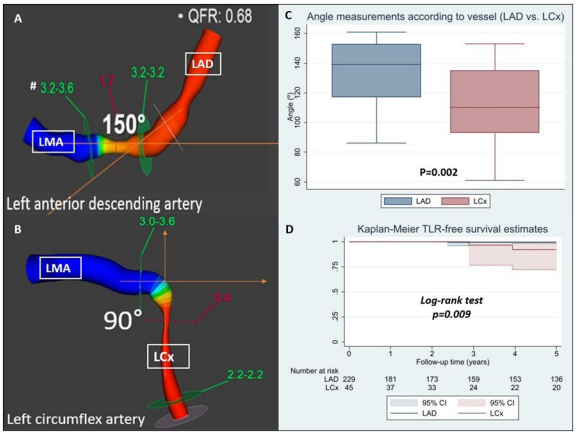

Figure 1 Main figure. (A) Example of LAD–LMA angle offline 3D reconstruction (Medis Suite V.3.2.61.0) and angle measurement (150°). (B) Example of LCx–LMA angle offline 3D reconstruction and angle measurement (90°). (C) Boxplot, comparison of angle measurements according to vessel (LAD or LCx). (D) Kaplan-Meier TLR-free survival estimates at 5-year follow-up (LAD vs LCx); log-rank test, p=0.009. *, QFR; #, vessel diameter in millimetre. 3D, three-dimensional; LAD, left anterior descending artery; LCx, left circumflex artery; LMA, left main artery; QFR, quantitative flow ratio; TLR, target lesion revascularisation.

Bifurcation angle analysis method

Bifurcation angle parameters were measured with a validated program of three-dimensional (3D) angiographic analysis (Medis Suite V.3.2.61.0). These 3D images required two different cine-angiograms separated by more than 30°. Offline 3D reconstruction was performed by two experienced operators blinded to the study results. The angles between the LM and the LAD and the LM and LCx were measured following the 3D reconstruction (figure 1A,B).

Statistical analysis

The data are presented as mean (SD) for continuous variables with a normal distribution, median (IQR) for continuous variables with a non-normal distribution and as frequency (%) for categorical variables. Student's t-test and the Mann-Whitney U test were used to compare continuous variables with normal and non-normal distributions, when needed. The χ^2 test or Fisher's exact test was used to compare categorical variables. Univariable analysis was performed for quantitative variables and reported as ORs with 95% CI.

To evaluate different types of revascularisation events, patients with ostial LCx stenosis were compared with patients with ostial LAD stenosis. A score-matched cohort was created with a 1:1 ratio and nearest-neighbour match. Standardised mean differences (SMDs) were calculated for all covariates before and after the matching to assess for balance after matching. A good range of SMDs is less than 0.1 (in absolute value), and a suitable range would be between 0.1 and 0.25.[13 14]

Freedom from mortality curve was calculated using the Kaplan-Meier method, and comparison was obtained with the log-rank test. A Cox regression was built to identify independent predictors of TLR. Variables included in the model were selected according to their clinical relevance and plausible relationship with the studied outcomes. Statistically significant differences ($p<0.05$) were taken into account to guide variable selection.

All of the data were analysed using Stata V.16 and R statistical software V.3.3.2 (R Foundation).

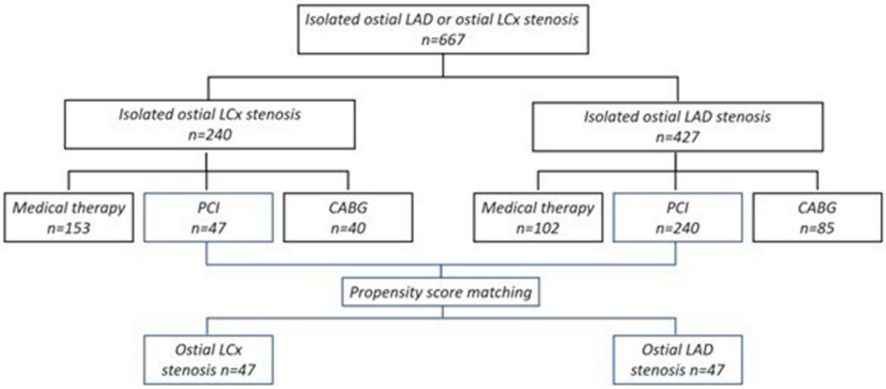

Figure 2 Flowchart. Patients with isolated ostial stenosis located in LAD or LCx detected in coronary angiographies performed between 2004 and 2018. CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCx, left circumflex artery; PCI, percutaneous coronary intervention.

Patient and public involvement

Patients or the public were not involved in the design of our research and recruitment to or conduct of the study.

RESULTS

From 2004 to 2018, a total of 667 of patients were diagnosed with isolated ostial stenosis located in LAD or LCx in our institution (figure 2). In the global population, patients in the LCx group were significantly older, had more stable angina and had more comorbidities. Differences between groups are displayed in online supplemental table 1. Medical treatment was used more frequently in the ostial LCx group than in the ostial LAD group (63% (153/240) vs 23.8% (102/427), p<0.001).

From these, 287 (43%) consecutive patients who underwent PCI for isolated ostial LAD (n=240) or ostial LCx (n=47, 7%) stenosis were included. Baseline characteristics of the unmatched population are shown in table 1. Patients from the LCx group were older and had a higher body mass index and higher rates of hypertension. In addition, the LCx group had a higher incidence of prior MI, previous revascularisation and multivessel disease.

After a propensity score, a total of 47 matched pairs were obtained. The mean age was 72±12 years and 82% (77/94) of patients were male. To the propensity score, the SMDs were calculated prematching and postmatching for studied variables between groups. Variables included and SMDs are depicted in the online supplemental tables 2 and 3. To see the success of the propensity score, we studied the SMD in online supplemental table 3. Distributional balance and overlap on covariates and propensity scores before and after matching are shown in online supplemental figure 1.

Baseline features following adjustment are depicted in table 2.

Procedural characteristics

Most of the lesions were treated with a stent implantation (94.6% (88)), of which 83% (73/88) were drug-eluting stents (DESs).

The most frequent interventional technique used was a single-stent technique (91.5% (43) in the LCx group and 93.6% (44) in the LAD group) in both groups. Ostial stenting was used in 83% (39) in the LCx group and 87% (41) in the LAD group without differences between groups. The rate of cross-over stenting technique was 7.4% (7/94), stenting LM into LAD in three cases and LM into LCx in four cases. A two-stent technique was used only in the LCx group (two lesions using a DK-crush and T-stenting technique, respectively). Regarding the type of stent used, seven patients had TLR in the LCx group, of which two were treated with bare-metal stent; one patient was treated with a first-generation DES; and four patients were treated with second-generation DES. In the LAD group, one patient had TLR and the stent implanted was first-generation DES. Procedural success of the index PCI was found in 98% (46) of cases in the LCx group and 91% (43) in the LAD group, and the reason for PCI failure was an uncrossable chronic total occlusion in all cases.

Bifurcation angle

Bifurcation angle parameters were measured in end-diastole frames before wiring the vessel. The angle between LM–LAD was significantly wider than the angle between the LCx–LM angle (128°±23° vs 108°±24° (p=0.002) (figure 1C and online supplemental table 3).

Moreover, a tendency to tighter angles was observed in patients with TLR (mean angle 100° vs 117.5° in non-TLR patients, p=0.09).

Clinical outcome at long-term follow-up

The median follow-up was 5.5 (1.5–9.3) years, and the follow-up was completed in all patients. The TLR was significantly higher in the LCx group compared with the LAD arm (15% (7/46) vs 2% (1/43)), p=0.02. The median time to TLR was 281days (IQR:105–412 days). The Kaplan-Meier curve for 5-year TLR-free survival (log-rank test p=0.009) is depicted in figure 1D. Interestingly, the TLR–LM involvement rate was 6.5% (3/46) in the LCx group, that is to say, 43% (3/7) of patients with restenosis, while no TLR–LM involvement was found in the LAD group. The LM involvement was managed by PCI with two-stent technique (culotte) in one case and with provisional stenting LM–LCx in the other two cases. In contrast, no differences in other relevant clinical parameters were observed between the two groups (table 3).

To identify predictors of TLR, a Cox regression model was performed. Variables included in the model are shown in table 4. The location of the lesion at ostial LCx was an independent predictor of TLR with a sevenfold increased risk (HR=7.5, 95% CI 2.1 to 26.4, p<0.001) (table 4).

Moreover, TLR rates according to clinically relevant subgroups are depicted in figure 3.

DISCUSSION

The main findings of this study were, first, the treatment most often used in isolated ostial LCx lesion is medical treatment. Second, percutaneous treatment of isolated ostial LCx had an

Table 1 Baseline characteristics (before matching)

Baseline characteristics	Total (N=287)	Ostial LCx (n=47)	Ostial LAD (n=240)	P value
Age (years), mean±SD	67±14	71±13	67±14	**0.034**
Female, n (%)	66 (23.0)	8 (17.0)	58 (24.2)	0.287
BMI, mean±SD	26±5	29±5	26±5	**0.002**
Cardiovascular risk factors, n (%)				
Hypertension	181 (63.1)	37 (78.7)	144 (60.0)	**0.015**
Dyslipidaemia	140 (48.8)	28 (59.6)	112 (46.7)	0.105
Diabetes	65 (22.7)	15 (32.0)	50 (20.8)	0.097
Smoking history	157 (54.7)	25 (53.2)	132 (55.0)	0.820
Previous history, n (%)				
Previous AMI	72 (25.1)	22 (46.8)	50 (20.8)	**<0.001**
Previous revascularisation	66 (23.4)	23 (48.9)	43 (18.3)	**<0.001**
Previous stroke	13 (4.5)	2 (4.3)	11 (4.6)	0.921
Peripheral vascular disease	26 (9.1)	5 (10.6)	21 (8.8)	0.680
CKD	29 (10.1)	9 (19.2)	20 (8.3)	**0.024**
Clinical presentation, n (%)				
Stable angina	68 (23.7)	15 (31.9)	53 (22.1)	0.290
NSTEMI	141 (49.1)	19 (40.4)	122 (50.8)	0.290
STEMI	78 (27.2)	13 (27.7)	65 (27.1)	0.290
Angiographic and procedural characteristics				
Multivessel disease, n (%)	158 (56.0)	33 (70.2)	125 (53.2)	**0.029**
Number of diseased vessels, n (%)				**0.013**
1	129 (44.9)	15 (31.9)	114 (47.5)	
2	103 (35.9)	16 (34.0)	87 (36.3)	
3	55 (19.2)	16 (34.0)	39 (16.3)	
Lesion length, mean±SD	13.8±6.7	12.6±6.0	14.0±6.8	0.210
% stenosis, mean±SD	87.0±11.9	87.6±10.6	86.8±12.1	0.711
IVUS/OCT, n (%)	38 (13.2)	9 (19.1)	29 (12.1)	0.191
2004–2008	7 (7.5)	1 (14.3)	6 (6.9)	
2009–2013	6 (5.8)	1 (4.8)	5 (6.1)	
2014–2018	27 (31.8)	7 (36.8)	20 (30.3)	
Calcification, n (%)	135 (47.0)	23 (48.9)	112 (46.7)	0.776
Plaque modification device, n (%)	22 (7.7)	5 (10.6)	17 (7.1)	0.393
Predilatation, n (%)	165 (63.7)	37 (78.7)	128 (60.4)	**0.018**
Stent implantation, n (%)	268 (93.4)	46 (97.9)	222 (92.5)	0.176
Second-generation drug-eluting stent, n (%)	174 (65.0)	28 (60.9)	146 (65.8)	0.405
Stent diameter (mm), mean±SD	3.2±0.4	3.1±0.5	3.2±0.4	**0.004**
Stent length (mm), mean±SD	16.8±6.6	15.5±6.7	17.1±6.5	0.142
Post dilatation, n(%)	201 (72.3)	38 (84.4)	163 (70.0)	**0.047**
Maximum diameter (mm), mean±SD	3.2±0.5	3.0±0.6	3.3±0.5	**0.010**
Kissing balloon technique, n (%)	6 (2.1)	6 (12.8)	0 (0.0)	**<0.001**
Angiographic success, n (%)	274 (95.5)	46 (97.9)	228 (95.0)	0.387

P-values set in bold indicate statistical significance.
*χ^2 test was performed on binary data, data expressed by absolute numbers and percentages; Fisher's test was performed in cases with n<5 in some groups. Student's t-test was performed on quantitative variables, data expressed by mean and SD.
AMI, acute myocardial infarction; BMI, body mass index; CKD, chronic kidney disease; IVUS, intracoronary vascular ultrasound; LAD, left descending anterior; LCx, left circumflex; NSTEMI, non-ST-elevation myocardial infarction; OCT, optical coherence tomography; STEMI, ST-elevation myocardial infarction.

increased rate of TLR compared with the treatment of ostial LAD at long-term follow-up. Moreover, no differences were observed in the rates of death or MI between groups. Likewise, the rate of TLR–LM was higher in the ostial LCx group at follow-up. Finally, we found anatomical differences between groups: the angle of the LM and LCx was significantly lower than the angle between LM and LAD.

Ostial LAD or LCx coronary lesions are a challenge for interventional cardiologists, as percutaneous treatment may somehow involve the distal LM. In our study, medical treatment was used more frequently in the ostial LCx group. Clinicians having already recognised the challenges of PCI for ostial LCx lesions may have selected patients with particularly refractory symptoms. On the other hand, patients in the LCx group were older and had more comorbidities and multivessel disease.

The optimal technique to treat ostial lesions remains controversial, particularly in treating ostial LCx lesions. Historically, the most commonly used approach in the treatment of isolated ostial LAD and LCx lesions was positioning the stent at the edge of the ostium.[15–17] However, this technique comes with the inherent risk of geographical miss or plaque shift into the LM. In addition, intracoronary imaging studies have shown that at

Table 2 Baseline characteristics (after matching)

Baseline characteristics	Total (N=94)	Ostial LCx (n=47)	Ostial LAD (n=47)	P value
Age (years), mean±SD	72±12	71±13	73±11	0.368
Female, n (%)	17 (18.1)	8 (17.0)	9 (19.1)	0.789
BMI, mean±SD	28±5	28±5	26±4	0.989
Cardiovascular risk factors, n (%)				
Hypertension	76 (80.8)	37 (78.7)	39 (83)	0.6
Dyslipidaemia	53 (56.4)	28 (59.6)	25 (53)	0.533
Diabetes	31 (33.0)	15 (31.9)	16 (34)	0.826
Smoking history	51 (54.3)	25 (53.2)	26 (55)	0.836
Previous history, n (%)				
Previous AMI	31 (33.0)	17 (36.2)	14 (29.8)	0.51
Previous revascularisation	45 (47.9)	23 (48.9)	22 (46.8)	0.836
Previous PCI	41 (43.6)	21 (44.7)	20 (42.6)	0.835
Previous CABG	10 (10.6)	6 (12.8)	4 (8.5)	0.503
Previous stroke	3 (3.2)	2 (4.3)	1 (2.1)	0.557
Peripheral vascular disease	8 (8.5)	5 (10.6)	3 (6.4)	0.46
CKD	16 (17.0)	9 (19.1)	7 (14.9)	0.583
Clinical presentation, n (%)				
Stable angina	30 (31.9)	15 (31.9)	15 (31.9)	0.737
NSTEMI	41 (43.6)	19 (40.4)	22 (46.8)	0.737
STEMI	23 (24.5)	13 (27.7)	10 (21.3)	0.737
ACS	64 (68.1)	32 (68.1)	32 (68.1)	>0.99
Angiographic and procedural characteristics				
Multivessel disease, n (%)	59 (62.8)	33 (70.2)	26 (55.3)	0.135
Number of affected vessels, n (%)				0.129
1	35 (37.2)	14 (29.8)	21 (44.7)	
2	35 (37.2)	17 (36.2)	18 (38.3)	
3	24 (25.5)	16 (34.0)	8 (17.0)	
Lesion length, mean±SD	14.0±7.0	12.6±6.0	15.2±7.6	0.088
% stenosis, mean±SD	85.5±11.6	87.6±10.6	83.7±12.2	0.118
IVUS/OCT, n (%)	13 (13.8)	10 (21.3)	3 (6.4)	**0.036**
2004–2008	1 (3.6)	1 (14.3)	0 (0.0)	
2009–2013	2 (5.4)	1 (4.8)	1 (6.3)	
2014–2018	10 (34.5)	7 (36.8)	3 (30.0)	
Calcium, n (%)	52 (55.3)	23 (48.9)	29 (61.7)	0.213
Plaque modification device, n (%)	5 (5.3)	5 (10.6)	0 (0.0)	**0.022**
Predilatation, n (%)	71 (75.5)	38 (80.9)	33 (70.2)	0.23
Stent implantation, n (%)	88 (94.6)	45 (97.8)	43 (91.4)	0.168
Second-generation drug-eluting stent, n (%)	55 (62.5)	29 (64.4)	26 (60.5)	0.355
Stent diameter (mm), mean±SD	3.0±0.4	3.0±0.3	3.0±0.5	0.89
Stent length (mm), mean±SD	16.4±6.5	15.5±6.7	17.4±6.3	0.158
Post dilatation, n (%)	73 (79.4)	38 (84.4)	35 (74.5)	0.237
Maximum balloon diameter (mm), mean±SD	3.0±0.6	3.0±0.6	3.0±0.5	0.65
Kissing-balloon technique, n (%)	8 (8.6)	6 (13.0)	2 (4.3)	0.101
Angiographic success, n (%)	89 (94.7)	46 (97.9)	43 (91.5)	0.168
PCI technique, n (%)				
Balloon (without stenting)	2 (2.1)	1 (2.1)	1 (2.1)	–
One-stent technique				
Ostial stent	80 (85.0)	39 (83.0)	41 (87.2)	0.562
Cross-over technique	7 (7.4)	4 (8.5)	3 (6.4)	>0.99
Two-stent technique	2 (2.1)	2 (4.3)	0 (0.0)	0.495
T-stenting	1 (1.0)	1 (2.1)	0 (0.0)	>0.99
DK-crush	1 (1.0)	1 (2.1)	0 (0.0)	>0.99

P-values set in bold indicate statistical significance.
*χ^2 test was performed on binary data, data expressed by absolute numbers and percentages; Fisher's test was performed in cases with n<5 in some groups. Student's t-test was performed on quantitative variables, data expressed by mean and SD.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DK-crush, double kissing crush; IVUS, intracoronary vascular ultrasound; LAD, left descending anterior; LCx, left circumflex; NSTEMI, non-ST-elevation myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 3 Results (after matching)

Endpoints	LCx (n=47)	LAD (n=47)	OR (95% CI)	P value
TLR, n (%)	**7 (14.9)**	**1 (2.1)**	**8.05 (0.95 to 68.26)**	**0.027**
TVR, n (%)	10 (21.3)	6 (12.8)	1.85 (0.61 to 5.58)	0.272
All-cause MI, n (%)	2 (4.3)	4 (8.5)	0.47 (0.08 to 2.74)	0.399
MI related to TLR, n (%)	1 (2.1)	0 (0)	–	0.315
All-cause death, n (%)	19 (40.4)	22 (46.8)	0.77 (0.34 to 1.74)	0.533
Cardiac death, n (%)	10 (21.3)	14 (29.8)	0.62 (0.25 to 1.63)	0.344
TLF, n (%)	14 (29.8)	15 (31.9)	0.91 (0.38 to 2.17)	0.823
MACETVR, n (%)	25 (53.2)	28 (59.6)	0.77 (0.34 to 1.75)	0.533
MACETLR, n (%)	23 (48.9)	26 (55.3)	0.77 (0.34 to 1.74)	0.536

MACE includes all-cause death, MI, TLR and TVR. TLF includes TLR, MI related to TLR and cardiac death. MACETVR includes all-cause death, MI and TVR. MACETLR includes all-cause death, MI and TLR.
P-values set in bold indicate statistical significance.
*Logistic regression.
LAD, left anterior descending artery; LCx, left circumflex; MACE, major adverse cardiovascular event; MACETLR, major adverse cardiovascular event target lesion revascularisation; MACETVR, major adverse cardiovascular event target vessel revascularisation; MI, myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

very acute angles between the LM and the CX, it is impossible to adjust the stent to the ostium without a floating strut within the LM. The LM distortion due to balloon dilatation may be one of the theoretical reasons explaining this finding.

The interventional technique used in the present study was ostial stenting in more than 80% of cases with no differences between both groups. In a previous study, ostial LAD lesions treated with cross-over stenting from the LM to LAD appeared to have superior results when compared with ostial stenting in terms of a reduction in TVR.[8] However, in isolated LCx ostial lesions, there is a paucity of data to support any recommendations. Most operators try to avoid using a bifurcation technique that would jail the LAD, as typically this vessel supplies a greater territory of myocardium compared with the LCx[18] For this reason, the most commonly used technique in this study was to adjust the stent to the ostium. However, irrespective of the vessel treated with a cross-over technique, the rates of TLR at the LCx ostium have been shown to be higher than those in ostial LAD lesions.[10] With this in mind, the bifurcation consensus recommends cross-over stenting (covering the involved ostial LAD or ostial LCx and the diseased segment of LM) unless the anatomy is particularly favourable (rectangular angle between LAD–LCx, perfect visualisation of SB take-off and non-diseased LM).[7] In our study, no TLR was observed in patients treated with cross-over technique in both groups.

Table 4 Cox regression for TLR (global population, n=287)

	HR	CI 95%	P value
Ostial LCx PCI	7.49	2.12 to 26.41	**<0.001**
Age (years old)	1.01	0.96 to 1.06	0.677
Body mass index (kg/m^2)	1.04	0.94 to 1.14	0.465
Hypertension	0.35	0.10 to 1.20	0.095
Diabetes mellitus	3.25	0.72 to 14.57	0.124
Chronic kidney disease	4.00	0.67 to 23.79	0.129
Multivessel disease	1.87	0.59 to 6.00	0.288
Prior PCI	1.65	0.55 to 4.94	0.374
Stent diameter	1.55	0.41 to 5.90	0.517

P-values set in bold indicate statistical significance.
*Cox regression.
LCx, left circumflex; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation.

Another aspect to take into account is that angiography underestimates the extent of LM bifurcation atherosclerosis[8]; therefore, it is advisable to use intracoronary imaging to confirm isolated LAD–LCx stenosis prior to considering ostial stenting. In the present study, the use of intracoronary imaging was low at only 13%; however, its use was more frequent in the LCx group. One of the reasons for the low use of this technique was that 70% of patients were treated prior to 2014, preceding a formal recommendation in the guidelines for the use of coronary imaging to optimise stent implantation.[19 20] In fact, when the intracoronary imaging rate was analysed according to procedural date, this rate reached to 35% between 2014 and 2018. In our study, patients with intracoronary vascular ultrasound (IVUS)-guided PCI had no TLR.

An interesting finding of this study was the observation of LM–TLR of 43% in the LCx group that it seems intimately related to the ostial stent technique. There are several reasons for this finding: the very low use of intracoronary imaging and consequently the inaccurate assessment of the amount of plaque in the LM at baseline and the lack of certainty of the precise final position of the stent that may not cover the ostium completely.

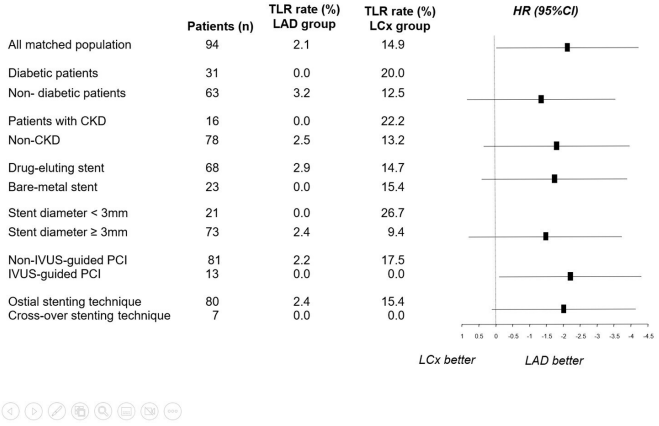

Figure 3 Different analyses for TLR rates according to subgroups. CKD, chronic kidney disease; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex artery; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation.

Second, as was previously described, manipulation and delivery of equipment may lead to future accelerated disease.[21]

It is interesting to point out the anatomical differences between the ostium of the LCx and LAD that may influence the poorer clinical outcomes observed in the LCx group. In our study, the angle between the LM and the CX was significantly lower than the angle between LM and LAD. Our results correlate with previous studies that have shown distal LM bifurcation angles measured by multislice CT or 3D quantitative coronary angiography, which observed that the LM–LCx had tighter angles compared with the LM–LAD. This tighter angle may explain the increased rates of TLR observed in the present study. Amemiya *et al* studied patients with unprotected LM bifurcation lesions treated with single cross-over LM–LAD stenting, and significantly higher incidence of MACE was observed in the group with the lower angle.[22] In addition, angle differences may lead to different shear wall stress and rheology, which are factors related to the appearance of neointimal hyperplasia.[23] Another factor that may be involved is the potential modification of the bifurcation geometry, which may be more prevalent in bifurcations with more acute angles than in those with a wider angle, and this may explain the differences between ostial LAD and LCx shown in this study. Likewise, the systolic and diastolic variations during cardiac motion may also vary after stent implantation. At the hinge point of an acute angulation, more frequently observed in LM–LCx, stents may be more subjected to torsion, flexion and rotational forces that may increase the risk of restenosis at this location.[10]

Limitations

The main limitation of this study is that this is a small, single-centre non-randomised cohort, and therefore our observation are hypothesis-generating. In addition, due to confounders and the retrospective nature of the study, despite the propensity matching, reaching any conclusion is difficult. Larger prospective cohorts could eventually allow drawing more definitive conclusions. Isolated ostial LCx lesions are infrequent. The incidence of ostial stenosis in general ranges from 0.13% to 2.7%, and in the majority of cases, there is a coexisting disease in the multiple coronary vessel which explains the slow enrolment of patients. In addition, despite the fact that using an ostial LAD stenting technique is no longer recommended, the percentage of the use of this technique was similar in both groups. The best interventional approach for this patient cohort must be assessed in larger dedicated studies. One of the main limitations is the lack of certainty of covering the ostium completely with the ostial stenting technique, particularly with the very low use of intracoronary imaging, which may influence the LM progression observed in this study.

In conclusion, this is the first study that compares the clinical outcomes of percutaneous treatment of ostial LCx versus ostial LAD in a matched population. Isolated ostial LCx lesions have an increased risk of TLR in comparison with lesions located at the ostium of the LAD. There are also anatomical differences with regard to the angle between the LM and the LCx or LAD. It seems that the differences in geometrical and rheological characteristics of both locations may play a role in these findings. Larger studies are needed to confirm these results.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study has been conducted in accordance with the Declaration of Helsinki principles and Good Clinical Practice guidelines. Epidemiological and clinical data were obtained from electronic medical records, and the data were stored in an anonymised fashion. Informed consent was not obtained due to the design of the study.

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Supplementary table 1: Baseline characteristics of global population (Including medical, surgical and percutaneous treatment).

SUPPLEMENTARY TABLE 1: BASELINE CHARACTERISTICS OF GLOBAL POPULATION (Including medical, surgical and percutaneous treatment)				
BASELINE CHARACTERISTICS	**Total (n=667)**	**Ostial LCx (n=240)**	**Ostial LAD (n=427)**	***p***
Age (years), mean±SD	69.1±12.2	71.4 ±10.8	67.8±12.8	**<0.001**
Female, n (%)	165 (24.7)	65 (27.1)	100 (23.3)	0.277
BMI, mean±SD	27.1±4.9	27.7±4.8	26.9±4.9	**0.046**
CARDIOVASCULAR RISK FACTORS				
Hypertension, n(%)	461 (68.9)	182 (75.8)	279 (65.0)	**0.004**
Dyslipidemia, n(%)	355 (53.1)	137 (57.1)	218 (50.8)	0.119
Diabetes, n(%)	220 (32.9)	89 (37.1)	131 (30.5)	0.084
Smoking history, n(%)	333 (49.9)	111 (46.3)	222 (52.0)	0.155
PREVIOUS HISTORY				
Previous AMI, n(%)	302 (45.2)	139 (60.6)	163 (38.2)	**<0.001**
Previous PCI, n(%)	132 (19.7)	64 (26.7)	68 (15.9)	**0.001**
Previous stroke, n(%)	57 (8.5)	22 (9.2)	35 (8.2)	0.654
Peripheral vascular disease, n(%)	72 (10.8)	26 (10.8)	46 (10.7)	0.965
CKD, n(%)	84 (12.6)	36 (15.0)	48 (11.2)	0.154
CLINICAL PRESENTATION AND ANGIOGRAPHIC CHARACTERISTICS				
Acute coronary syndrome, n(%)	436 (65.3)	144 (60.0)	292 (68.3)	**0.031**
Stable angina, n(%)	288 (43.2)	122 (50.8)	166 (38.9)	**0.005**
Severe multivessel disease, n(%)	328 (49.2)	139 (57.9)	189 (44.3)	**0.001**

LCx: left circumflex; LAD: left descending anterior; SD: standard deviation; BMI: body mass index; AMI: acute myocardial infarction; PCI**: percutaneous coronary intervention;** CKD: chronic kidney disease**.**

Chi square test was performed to binary data, data expressed by absolute numbers and percentages; Fisher test was performed in cases with n<5 in some group. Student's t-test was performed to quantitative variables, data expressed by mean and standard deviation.

Supplementary table 2: standardized mean differences between groups Pre-matching.

	LAD (240)	LCx (47)	SMD
Dilated lesion (mean (SD))	0.82 (0.39)	0.87(0.34)	0.146
Sex (mean (SD))	0.24 (0.43)	0.17(0.38)	0.181
Age (mean (SD))	66.46(13.57)	71.13 (12.60)	0.357
Body mass index (mean (SD))	26.00(4.93)	28.50(5.40)	0.483
Prior CABG (mean (SD))	0.02(0.14)	0.13 (0.34)	0.411
Prior MI (mean (SD))	0.21 (0.41)	0.47(0.50)	0.562
Prior PCI (mean (SD))	0.18 (0.38)	0.43(0.50)	0.560
Arterial hypertension (mean (SD))	0.60(0.49)	0.79(0.41)	0.420
Hyperlipidaemia (mean (SD))	0.46(0.50)	0.60(0.50)	0.268
Diabetes mellitus (mean (SD))	0.21(0.41)	0.32(0.47)	0.247
Smoking (mean (SD))	0.55(0.50)	0.53(0.50)	0.045
Peripheral vascular disease (mean (SD))	0.09(0.28)	0.11(0.31)	0.061
Prior stroke (mean (SD))	0.05(0.21)	0.04(0.20)	0.018
CKD (mean (SD))	0.08(0.28)	0.19(0.40)	0.313
Acute coronary syndrome (mean (SD))	0.79(0.41)	0.68(0.47)	0.237
ACS type (mean (SD))	1.06(0.70)	0.96(0.78)	0.137
Prior PCI with stent (mean (SD))	0.92(0.26)	0.87(0.34)	0.172
Prior 1 lesion PCI (mean (SD))	0.62(0.49)	0.49(0.51)	0.259
Procedural success (mean (SD))	0.95(0.22)	0.94(0.25)	0.057
Prior stent (mean (SD))	0.91(0.28)	0.96(0.20)	0.185

LAD: left anterior descending, LCX: left circumflex, SMD: standardized mean differences, SD: standard deviation, CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention, CKD: chronic kidney disease. ACS: acute coronary syndrome.

Supplementary table 3: standardized mean differences post-matching.

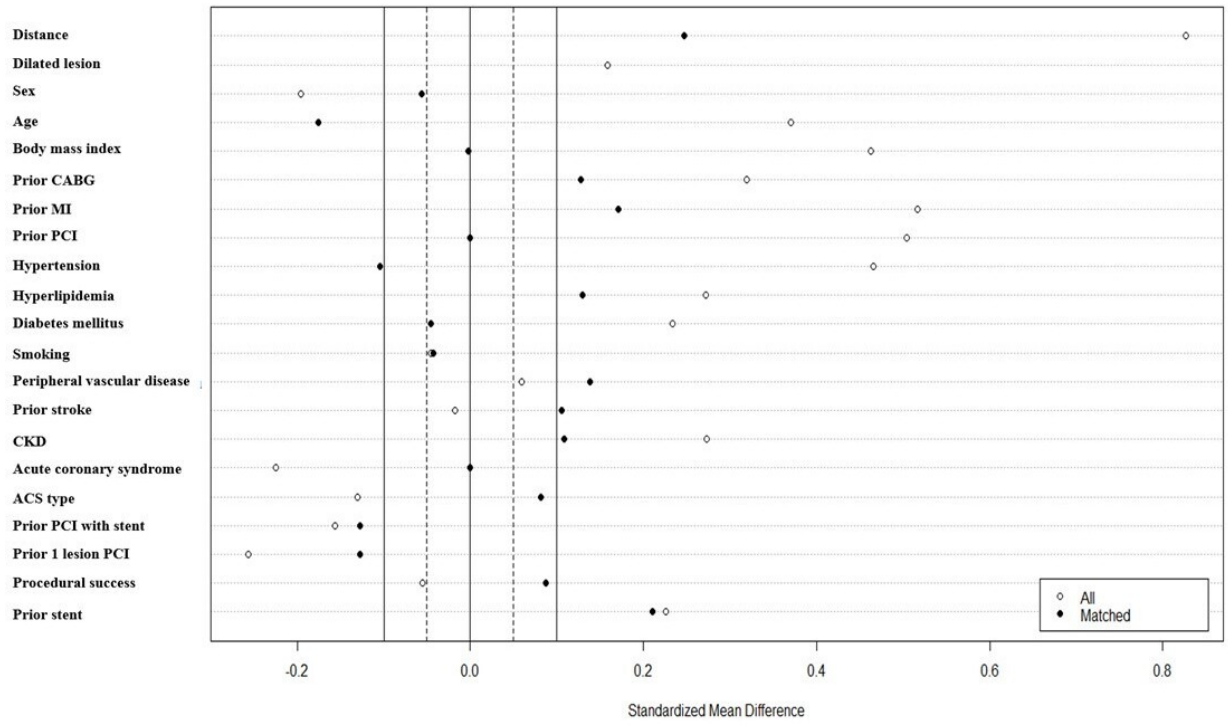
	Means LAD	Means LCx	Std. Mean Diff.	p-value (difference between groups)
DISTANCE	0.3409	0.278	0.2466	
Dilated lesion (mean (SD))	0.8723	0.9787	-0.3188	0.05158
Sex (mean (SD))	0.1702	0.1915	-0.0566	0.7914
Age (mean (SD))	71.1277	73.3404	-0.1756	0.3681
Body mass index (mean (SD))	28.5001	28.512	-0.0022	0.9899
Prior CABG (mean (SD))	0.1277	0.0851	0.1275	0.5087
Prior MI (mean (SD))	0.4681	0.383	0.1706	0.4095
Prior PCI (mean (SD))	0.4255	0.4255	0	>0.99
Arterial hypertension (mean (SD))	0.7872	0.8298	-0.104	0.6047
Hyperlipidaemia (mean (SD))	0.5957	0.5319	0.1301	0.5377
Diabetes mellitus (mean (SD))	0.3191	0.3404	-0.0456	0.8286
Smoking (mean (SD))	0.5319	0.5532	-0.0426	0.8381
Peripheral vascular disease (mean (SD))	0.1064	0.0638	0.138	0.4652
Prior stroke (mean (SD))	0.0426	0.0213	0.1054	0.5624
CKD (mean (SD))	0.1915	0.1489	0.1081	0.5878
Acute coronary syndrome (mean (SD))	0.6809	0.6809	0	>0.99
ACS type (mean (SD))	0.9574	0.8936	0.0819	0.6827
Prior PCI with stent (mean (SD))	0.8723	0.9149	-0.1275	0.5087
Prior 1 lesion PCI (mean (SD))	0.4894	0.5532	-0.1277	0.5407
Procedural success (mean (SD))	0.9362	0.9149	0.087	0.6982
Prior stent (mean (SD))	0.9574	0.9149	0.2108	0.4044

LAD: left anterior descending, LCX: left circumflex, Std. Mean Diff.: standardized mean differences, SD: standard deviation, CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention, CKD: chronic kidney disease. ACS: acute coronary syndrome.

Supplementary table 4: Differences in bifurcation angle with LMCA according to vessel (LAD vs. LCx)

Differences in bifurcation angle with LMCA according to vessel (LAD vs. LCx) P=0.002			
	n	**Mean ± SD**	**CI95%**
Angle LAD-LMCA (º)	23	128.4 ±22.9	118.5-138.3
Angle LCx-LMCA (º)	34	107.5 ±23.5	99.3-115.7

LMCA*: left main coronary artery;* ***LAD****: left anterior descending;* ***LCX****: left circumflex;* ***SD****: standard deviation;* ***CI****: confidence interval.*
#Student's t-test, data expressed by mean and standard deviation.


Distance
Dilated lesion
Sex
Age
Body mass index
Prior CABG
Prior MI
Prior PCI
Hypertension
Hyperlipidemia
Diabetes mellitus
Smoking
Peripheral vascular disease
Prior stroke
CKD
Acute coronary syndrome
ACS type
Prior PCI with stent
Prior 1 lesion PCI
Procedural success
Prior stent
All
Matched
-0.2
0.0
0.2
0.4
0.6
0.8
Standardized Mean Difference