

# Circulation: Cardiovascular Interventions

# **ORIGINAL ARTICLE**

# Patterns of Restenosis After Left Main Bifurcation Single- or Dual-Stenting: An EBC MAIN Trial Subanalysis

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**BACKGROUND:** In the randomized EBC MAIN trial (European Bifurcation Club Left Main Coronary Stent), target lesion revascularization at 3 years poststenting of left main (LM) bifurcations was more frequent with upfront dual-stenting compared with the stepwise provisional approach. Restenosis location and its relation to stent technique are poorly characterized. The aim of this study was to investigate restenosis location after LM bifurcation stenting, and the impact of stent implantation technique.

METHODS: Patients from the EBC MAIN trial who underwent target lesion revascularization during the 3-year follow-up had restenosis location assessed by the core laboratory. Restenosis was defined as ≥50% lesion diameter stenosis.

**RESULTS:** Among 48 patients with target lesion revascularization (mean age 70.3±10.6 years, 72.9% men), 31 were randomized to and treated with upfront dual-stenting, while 17 were randomized to the stepwise provisional technique, of whom 4 had dual-stent implantation. The treatment groups therefore comprised 35 dual-stented and 13 single-stented patients. The commonest pattern of subsequent restenosis was isolated ostial circumflex restenosis (58% of patients), regardless of dual- or single-stent implantation. The ostial circumflex was the culprit lesion for target lesion revascularization in 34 (71%) patients overall (dual- versus single-stented patients: 77% versus 54%; *P*=0.115). During the 3-year follow-up, the mean % diameter stenosis at the circumflex ostium was similar after dual- versus single-stent implantation (64.6% versus 60.5%, coefficient, —0.12 [95% CI, —0.46 to 0.22]; *P*=0.473). Single stenting from LM to the circumflex artery was associated with worse subsequent mean % diameter stenosis in the ostium of the left anterior descending artery versus single stenting from LM- left anterior descending (49.8% versus 19.8%, coefficient, 0.57 [95% CI, 0.003–1.13]; *P*=0.049).

**CONCLUSIONS:** The circumflex ostium is the commonest site requiring revascularization after LM bifurcation stenting, irrespective of whether 1 or 2 stents were deployed. Strategies are needed to improve the long-term success of percutaneous coronary intervention to the circumflex artery ostium.

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# See Editorial by Rab

#### WHAT IS KNOWN

 In the EBC MAIN (European Bifurcation Club Left Main Coronary Stent) randomized trial, target lesion revascularization at 3 years poststenting of left main bifurcations was more frequent with upfront dualstenting compared with a stepwise provisional approach.

## WHAT THE STUDY ADDS

- After left main bifurcation percutaneous coronary intervention in the EBC MAIN trial, the circumflex ostium was the commonest site requiring revascularization.
- The circumflex ostium was the commonest site requiring revascularization after left main bifurcation percutaneous coronary intervention, irrespective of whether one or two stents had been deployed.
- Strategies are still needed to improve the long-term success of percutaneous coronary intervention to the circumflex artery ostium.

eft main (LM) bifurcation percutaneous coronary intervention (PCI) is an effective alternative to coronary artery bypass graft surgery, especially in patients with low or intermediate SYNTAX (Synergy Between PCI witth Taxus and Cardiac Surgery) scores. However, LM bifurcation PCI constitutes a challenge for interventional cardiologists, because of the large amount of subtended myocardium at risk if results are suboptimal.

In the EBC MAIN (European Bifurcation Club LM Coronary Stent) randomized trial, target lesion revascularization (TLR) occurred more frequently with an upfront dual-stent strategy compared with a stepwise provisional approach for LM bifurcation PCI during the 3-year follow-up (15.6% versus 8.3%; *P*=0.014).² Prior registries demonstrated higher rates of TLR with dual-stent compared with singlestent implantation for LM PCI, driven by circumflex (Cx) ostium restenosis.<sup>3,4</sup> Other predictors of in-stent restenosis after LM PCI include calcification, true bifurcation disease, insulin-dependent diabetes, stent under expansion, and smaller minimal stent area, whereas the proximal optimization technique above the carina to improve stent conformation to bifurcation geometry, and larger mean luminal vessel diameter reduce in-stent restenosis.<sup>5-7</sup>

Technological advancements in stents and pharmacotherapy have improved PCI outcomes. However,

# **Nonstandard Abbreviations and Acronyms**

Cx EBC MAIN	circumflex European Bifurcation Club Left Main Coronary Stent
LAD	left anterior descending
LM	left main
NC	noncompliant
PCI	percutaneous coronary intervention
TAP	T and small protrusion
TLR	target lesion revascularization

restenosis continues to be problematic, and its location and relation to stent technique after contemporary PCI are not well characterized. Optimization of the index revascularization strategy could improve outcomes by avoiding future repeat invasive procedures and potentially myocardial infarction. In this subanalysis from the EBC MAIN trial, we investigated patterns of restenosis location in patients who underwent TLR after contemporary LM bifurcation PCI, and investigated any difference between dual- and single-stent implantation.

## **METHODS**

## Study Design and Population

The EBC MAIN trial<sup>8</sup> was an investigator-led, multicenter randomized trial in 11 European countries, comparing clinical outcomes in 467 patients with stable or acute coronary syndromes who had LM true bifurcation disease (Medina 1,1,1 or 0,1,1), with both branches >2.75 mm. Patients were enrolled from 2016 to 2019. A Clinical Research Organization (Cardiovascular European Research Center [CERC], Massy, France) provided trial oversight. The trial was registered on ClinicalTrials.gov (NCT02497014) and complied with the Declaration of Helsinki. The study protocol was approved by the relevant authorities in all countries involved in the study. The participants provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Details of the eligibility criteria are in Table S1. Patients were randomized, with an allocation ratio of 1:1, to a provisional stepwise approach, or an upfront dual-stent strategy, with second-generation Resolute Onyx drug-eluting stents (Medtronic, Minneapolis, MN). For the current subanalysis, an

as-treated analysis was performed, to compare patients treated with dual-stenting to patients who had single-stent implantation. Details of the PCI procedural steps, protocol, and eligibility criteria have been published previously, and are summarized in the Supplemental Methods. Intravascular ultrasound or optical coherence tomography were undertaken at the discretion of the operator.

#### **End Points**

The primary end point for EBC MAIN was a composite of allcause death, myocardial infarction, and TLR at 12 months. The individual components of the primary end point were secondary end points. Follow-up was at 6 months, and at 1 and 3 years. Events were adjudicated by an independent Clinical Events Committee, blinded to treatment randomization. Decisions to perform invasive angiography during follow-up were made by local clinicians, based on ischemic symptoms and positive noninvasive tests for ischemia. TLR referred to repeat revascularization with either balloon angioplasty, stenting, or coronary artery bypass graft surgery within the previously treated vessel area, or within 5 mm adjacent to this. Patients who underwent TLR and had information available on restenosis location were included in this analysis. For patients who had >1 angiogram during the 3-year follow-up, only the first angiogram was considered.

# Quantitative Coronary Angiography

Quantitative coronary angiography was performed by a core laboratory (CERC, Massy, France), using CAAS 7.3 software (Pie Medical Imaging, Maastricht, the Netherlands). Restenosis was defined as ≥50% lesion diameter stenosis. The 6-segment model (Figure S1) was used to record lesion % diameter stenosis at the following locations: proximal LM; distal LM; ostial Cx; proximal (nonostial) Cx; ostial left anterior descending (LAD) artery; and proximal (nonostial) LAD.

#### Statistical Analysis

Data are presented as mean $\pm$ SD, median and interquartile ranges, or proportions. Intergroup comparisons were made using a Student t test, Mann-Whitney U test, Pearson  $\chi^2$  test, or Fisher exact test.

For the association with lesion % diameter stenosis at the Cx ostium, multivariable linear regression models only adjusted for the following a priori determined clinically relevant covariates to prevent model overfitting: coronary calcification ≥moderate versus mild<sup>9</sup> kissing inflation exclusively with noncompliant (NC) balloons;<sup>10</sup> dual- versus single-stent implantation;<sup>11</sup> and bifurcation angle between the LAD and Cx arteries >median (ie, 70°) versus ≤median.<sup>12</sup> There was no imputation for missing values.

All tests were 2-tailed, and a P value of <0.05 was considered statistically significant. Data were analyzed using SPSS (version 29.0).

# **RESULTS**

## **Population**

During 3-year follow-up, 56 (12%) of the 467 patients in the EBC MAIN trial presented with a first restenosis

affecting the LM, Cx (ostial or proximal), or LAD (ostial or proximal), requiring TLR. The follow-up coronary angiograms were missing in 8 patients and these patients were excluded from the analysis. Information about the location of coronary restenosis was available in 48 (86%) patients who underwent TLR, and those patients were included in our analysis. The included patients were enrolled from 18 centers, in 9 European countries (age, 70.3±10.6 years, 35 (72.9%) men; Tables 1 and 2; Table S2). All patients had PCI with Resolute Onyx (Medtronic, Minneapolis, MN) drug-eluting stents. The median time interval between the initial LM bifurcation PCI procedure and the angiogram showing restenosis was 215 (interquartile range, 178–427) days.

Among the 48 patients included in the analysis, 31 were randomized to and treated with upfront dual-stenting, while 17 were randomized to the stepwise provisional technique. Among the 17 patients randomized to the stepwise provisional technique 13 were treated with single-stent implantation (5 had LM-Cx single-stenting and 8 had LM-LAD single-stenting) and 4 were treated with dual-stent implantation (2 patients had Culotte and 2 patients had T-stenting or T and small protrusion [TAP]). The treatment groups therefore comprised 35 dual-stented and 13 single-stented patients. The dual-stenting techniques performed were Culotte in 57.1%, T/TAP stenting in 37.1%, and Crush in 5.7%.

#### **Patterns of Restenosis**

Among the 48 patients included in the analysis, stent thrombosis was detected at the time of TLR in 5 patients. The mean % diameter stenosis in the culprit lesion for TLR was 72.9±13.2%. The distribution of restenosis is shown in Figures 1 and 2 and Table S3. Isolated ostial Cx coronary artery restenosis was the most frequent pattern of restenosis, regardless of whether a dual- or singlestent strategy was performed (58.3% [n=31] overall, 60.0% [n=24] for dual-stent, 53.8% [n=7] for singlestent implantation; Figure 1). Overall, isolated restenosis of the distal LM occurred in 12.5% of patients, and of the ostial LAD in 6.3% of patients (Figure 1). The ostial circumflex was the culprit lesion for TLR in 34 patients (70.8%) overall, 27 (77.1%) patients treated with dualstent implantation and 7 (53.8%) patients treated with single-stent implantation (P=0.115). Of these 34 patients, the TLR treatment strategy was PCI in 29 patients and coronary artery bypass graft surgery in 3 patients (missing data for 2 patients).

The mean % lesion diameter stenosis at the Cx ostium was  $61.6\pm23.6\%$  overall, and was similar in patients treated with dual-stent implantation  $(60.5\pm23.0\%)$  compared to single-stent implantation  $(64.6\pm25.8\%)$  (coefficient, -0.12 [95% CI, -0.46 to 0.22], P=0.473; Figure 2). Similar findings were demonstrated when an intention-to-treat analysis was performed (according to treatment

Table 1. Baseline Characteristics of Patients Who Had TLR During 3-Year Follow-Up After LM Bifurcation PCI in the EBC MAIN Trial, According to Treatment With Dual- or Single-Stenting

Characteristic	All patients with TLR (N=48)	Patients treated with dual-stent implantation (n=35)	Patients treated with single-stent implantation (n=13)	P value		
Randomized to dual-stent, %	31 (64.6)	31 (88.6)	0			
Randomized to single-stent, %	17 (35.4)	4 (11.4)	13 (100.0)			
Age, y; mean±SD	70.3±10.6	70.5±10.6	69.9±10.8	0.872		
Male, %	35 (72.9)	25 (71.4)	10 (76.9)	0.703		
Diabetes, %	24 (50.0)	16 (45.7)	8 (61.5)	0.330		
Ischemic symptoms, %	46 (95.8)	33 (94.3)	13 (100.0)	0.379		
Positive noninvasive imaging for ischemia, %	21 (43.8)	13 (37.1)	8 (61.5)	0.130		
Syntax score, %						
≤22	23 (47.9)	13 (37.1)	4 (30.8)			
>23	17 (35.4)	18 (51.4)	5 (38.5)			
Missing	8 (16.7)	4 (11.4)	4 (30.8)			
Medina classification (%)						
1,1,1	42 (87.5)	29 (82.9)	13 (100.0)			
0,1,1	6 (12.5)	6 (17.1)	0			
Adverse lesion features (%)						
Trifurcation	2 (4.2)	1 (2.9)	1 (7.7)	0.457		
Calcification ≥moderate	25 (52.1)	19 (54.3)	6 (46.2)	0.616		
Tortuosity ≥moderate	7 (14.6)	5 (14.3)	2 (15.4)	0.887		
Angle between LAD & Cx (%)				0.170		
>70°	21 (43.8)	14 (40.0)	7 (53.8)			
≤70°	25 (52.1)	21 (60.0)	4 (30.8)			
Missing	2 (4.2)	0	2 (15.4)			

Cx indicates circumflex; EBC MAIN, European Bifurcation Club Left Main Coronary Stent; LAD, left anterior descending; LM, left main; PCI, percutaneous coronary intervention; and TLR, target lesion revascularization.

randomized), and for analyses restricted to patients treated with Culotte versus single-stenting, and T-stenting or TAP versus single-stenting (Tables S4 through S6).

The mean % lesion diameter stenosis at the LAD ostium was  $28.3\pm26.3\%$  overall, and was comparable in patients treated with dual- or single-stenting ( $27.8\pm26.7\%$  and  $29.3\pm26.3\%$  respectively, coefficient, -0.03 [95% CI, -0.34 to 0.28]; Figure 2). The mean % lesion diameter stenosis at the distal LM was  $32.1\pm24.5\%$  overall, and again was similar in patients who had dual- or single-stenting performed ( $30.4\pm24.6\%$  and  $36.5\pm24.9\%$  respectively, coefficient, -0.11 [95% CI, -0.43 to 0.20]).

There was no association between the Cx ostium mean % diameter stenosis and the following: (1) dual- versus single-stent implantation; (2) kissing inflation exclusively with NC balloons versus kissing inflation with other balloons or no kissing inflation; (3) coronary calcification ≥moderate versus mild; and (4) bifurcation angle between the LAD and Cx arteries >70% versus ≤70% (Table S7).

Single-stenting from LM-Cx artery was associated with worse subsequent mean % diameter stenosis in the ostium of the LAD artery at 3 years versus single-stenting

from LM-LAD, after adjustment for kissing inflation with NC balloons ( $49.8\pm23.9\%$  versus  $19.8\pm22.4\%$ , coefficient, 0.57 [95% CI, 0.003–1.13]; P=0.049). In contrast, LM-LAD single-stenting compared to LM-Cx single-stenting was not associated with the mean % diameter stenosis for lesions at the Cx ostium ( $72.4\pm23.9\%$  versus  $49.0\pm25.0\%$ , coefficient, 0.36 [95% CI, -0.37 to 1.08]; P=0.292).

# **DISCUSSION**

The main findings of this study are:

- The Cx artery ostium was the most frequent location for TLR, 3 years after contemporary LM bifurcation PCI.
- The mean % diameter stenosis for lesions at the Cx ostium after LM bifurcation PCI, was not affected by: treatment with dual- versus single-stent implantation; kissing balloon inflation with NC balloons; coronary calcification; or bifurcation angle.
- Single-stenting from LM to Cx artery was associated with higher mean % diameter stenosis for lesions

Table 2. Baseline Procedural Characteristics of Patients Who Had TLR During 3-Year Follow-Up After LM Bifurcation PCI in the EBC MAIN Trial, According to Treatment With Dual- or Single-Stenting

Chavastaviatia	All patients with	Patients treated with dual-stent	Patients treated with single-stent	D. T.		
Characteristic	TLR (N=48)	implantation (n=35)	implantation (n=13)	P value		
Main vessel (%)	(== =)	()	- (- ( - )	0.365		
LM/LAD	34 (70.8)	26 (72.2)	8 (61.5)			
LM/Cx	14 (29.2)	9 (25.7)	5 (38.5)			
Type of preparation of LAD (%)						
Balloon	29 (60.4)	25 (71.4)	4 (30.8)	_		
Cutting balloon	5 (10.4)	3 (8.6)	2 (15.4)			
Rotablation	5 (10.4)	2 (5.7)	3 (23.1)			
Lithotripsy	1 (2.1)	0	1 (7.7)			
None	9 (18.8)	5 (14.3)	4 (30.8)			
Type of preparation of Cx (%)	1	1		0.700		
Balloon	29 (60.4)	23 (65.7)	6 (46.2)			
Cutting balloon	4 (8.3)	3 (8.6)	1 (7.7)			
Rotablation	7 (14.6)	4 (11.4)	2 (15.4)			
Lithotripsy	0	0	0			
None	9 (18.8)	5 (14.3)	4 (30.8)			
Stent technique used (%)						
Culotte	20 (41.7)	20 (57.1)	0			
Crush	2 (4.2)	2 (5.7)	0			
T-stenting or TAP	13 (27.1)	13 (37.1)	0			
Single-stent LM to LAD	8 (16.7)	0	8 (61.5)			
Single-stent LM to Cx	5 (10.4)	0	5 (38.5)			
Stent to LAD, %	43 (89.6)	35 (100.0)	8 (61.5)	<0.001		
Stent to Cx, %	40 (83.3)	35 (100.0)	5 (38.5)	<0.001		
Stent diameter LAD, mm; mean±SD	3.5±0.5	3.5±0.5	3.8±0.5	0.149		
Stent diameter Cx, mm; mean±SD	3.4±0.5	3.4±0.5	3.4±0.4	0.452		
Stent length LAD, mm; mean±SD	19.9±6.1	20.2±6.5	18.4±3.9	0.447		
Stent length Cx, mm; mean±SD	20.7±7.7	19.9±7.5	26.0±6.9	0.098		
TIMI flow in 2nd vessel after 1st stent (%)				0.557		
≤2	2 (4.2) 2 (5.8) 0					
3	43 (89.6)	30 (85.7)	13 (100.0)			
Missing data	3 (6.3)	3 (8.6)	0	+		
Reason for stenting side vessel in patients random		. ,				
Dissection	1 (5.9)	. , ,				
Residual stenosis	3 (17.6)					
Not applicable	13 (76.5)					
Kissing balloon inflation successful, %	46 (95.8)	35 (100.0)	11 (84.6)	0.018		
Kissing inflation exclusively with NC balloons, %	25 (52.1)	18 (51.4)	7 (53.8)	0.679		
POT done, %	45 (93.8)	33 (94.3)	12 (92.3)	0.801		
IVUS or OCT used, %	20 (41.7)	11 (31.4)	9 (69.2)	0.001		
LM lesion length, mm; mean±SD	5.5±2.1	5.1±2.0	6.8±2.2	0.018		
Livi restort terigui, tittii, meditado		35 (100.0)		0.014		
Successful result in LAD, %	48 (100.0)		13 (100.0)			

Cx indicates circumflex; EBC MAIN, European Bifurcation Club Left Main Coronary Stent; IVUS, intravascular ultrasound; LAD, left anterior descending; LM, left main; NC, noncompliant; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; POT, proximal optimization techniques; TAP, T and small protrusion; and TLR, target lesion revascularization.

in the LAD ostium compared to LM-LAD single-stenting, independent of kissing balloon inflation with NC balloons.

 Single stenting from LM to Cx artery compared to LM-LAD single-stenting was not associated with mean % diameter stenosis for lesions in the Cx ostium.

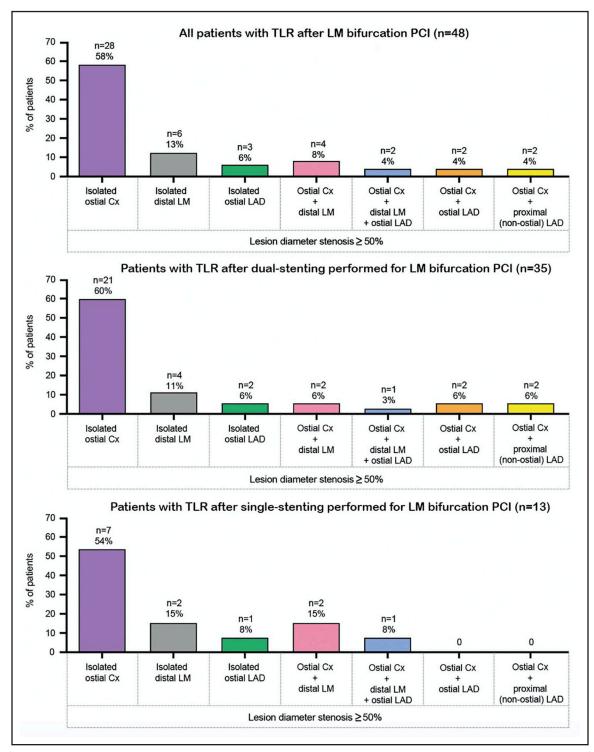


Figure 1. Angiographic patterns of restenosis with lesions ≥50% diameter stenosis, in patients undergoing target lesion revascularization (TLR) during 3-year follow-up after left main (LM) bifurcation percutaneous coronary intervention (PCI), according to dual- or single-stent implantation.

One patient had TLR without having lesions ≥50% diameter stenosis at follow-up-in that case the reason for TLR was acute coronary syndrome. Cx indicates circumflex; and LAD, left anterior descending.

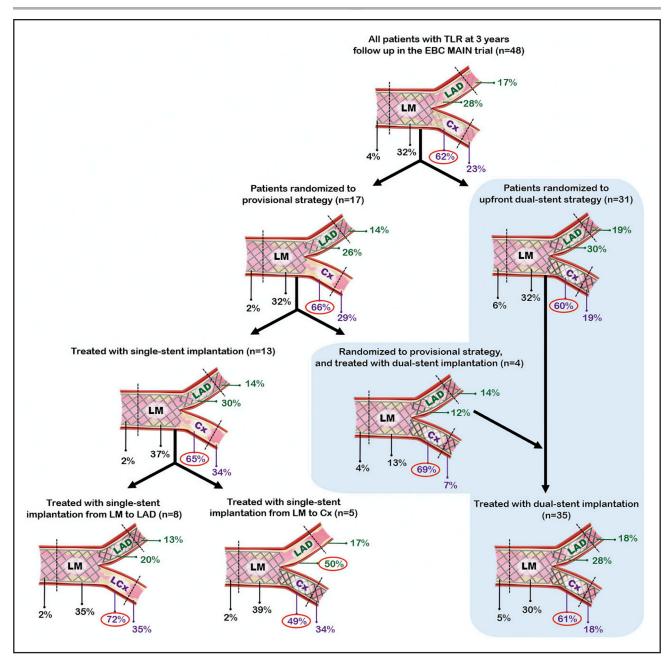


Figure 2. Coronary mean % diameter stenosis according to vessel segment location, for patients who needed target lesion revascularization (TLR) during 3-year follow-up in the EBC MAIN trial (European Bifurcation Club Left Main Coronary Stent). The mean % diameter stenoses are averages from the patients included in the study and not only from patients who had culprit lesions at each vessel location. Cx indicates circumflex; LAD, left anterior descending; and LM, left main.

After LM PCI with older generation stents, restenosis has been reported to occur in 7% to  $25\%^{3,4,6,13}$  of patients, and the Cx ostium was the commonest site for restenosis (48% to 60% of restenosed lesions). Despite PCI with a newer generation stent, we found similar rates of Cx ostium restenosis.

Our study shows that stent coverage of the Cx ostium does not protect from restenosis at this location. This is consistent with data from a previous study, which included patients with distal LM disease, and found that TLR rates at the Cx ostium were high irrespective of treatment with

a single-stent crossover technique from LM-Cx artery, or LM-LAD (83% versus 66%, respectively, *P*=0.39), whereas TLR rates at the LAD ostium were lower with LM-LAD single-stenting compared to LM-Cx single-stenting (21% versus 83%; *P*<0.001).¹⁴

The underlying mechanisms of Cx ostium restenosis are incompletely understood. Unique characteristics of the Cx ostium may predispose to increased risk of restenosis, for example, the Cx ostium often contains acute angulation, <sup>12</sup> which is associated with hinge-like motion during the cardiac cycle, <sup>15</sup> potentially predisposing to

stent fracture.<sup>16</sup> Further changes after stenting the Cx ostium that might increase the risk of restenosis include vessel straightening<sup>17</sup> and local shear stress change,<sup>18</sup> which may lead to local vessel wall injury and neointimal hyperplasia.<sup>19</sup> The Cx ostium is also the commonest location for stent under expansion,<sup>6</sup> because proximity to the aortic wall predisposes to recoil and rigidity, due to high elastic fiber content.<sup>12</sup> Furthermore, procedural factors including geographic miss and inadvertent longitudinal and radial stent deformation may also predispose to failure of PCI at the ostium of the Cx artery.

Compared with a stent strategy, a drug coated balloon to the Cx ostium might have advantages, because it combines mechanical expansion of the vessel, with reduction of neointimal hyperplasia, but without implanting a permanent scaffold, thereby maintaining the original coronary anatomy geometry and limiting inflammatory stimulation.<sup>20</sup> Importantly, however, drug coated balloon technology would only influence some of the factors that predispose the ostial Cx to restenosis. Future randomized trials are warranted to investigate a provisional strategy whereby the side branch ostium is dilated with a drug coated balloon, while the main vessel is stented, for LM true bifurcation disease. Ideally, such trials would involve angiographic follow-up with intracoronary imaging.

To explain the relatively high rates of culotte/TAP, a comparison between the EBC MAIN<sup>2</sup> and DKCRUSH-V<sup>21</sup> (Double Kissing Crush Versus Provisional T Stenting for Left Main Distal Bifurcation Lesions) trials is warranted. In DKCRUSH-V21 patients underwent LM bifurcation PCI with DK-crush, whereas in EBC MAIN patients randomized to dual-stenting underwent culotte PCI in 53% of cases, T-stenting/TAP in 32% of cases, and DK-crush in 5%.2 Despite both trials investigating LM bifurcation disease, the two trials treated anatomically distinct populations. First, patients with SYNTAX scores >32 comprised over 40% of the DKCRUSH-V trial, whereas patients with SYNTAX scores >32 were not recruited into EBC MAIN. Second, the mean main and side vessel lesion lengths were longer in DKCRUSH-V than in the EBC MAIN trial. Third, complex lesions, as per the DEFINITION criteria, 22 were more frequent in the DKCRUSH-V trial than in EBC MAIN. Available data suggest there is not one uniform approach for all LM bifurcation anatomy-DK-crush would be preferrable for more complex lesions, and the provisional technique for less complex disease.

Strengths of our study include the high follow-up rates for clinical events, core laboratory analyses, and independent adjudication of TLR events by a Clinical Events Committee. The main limitation is that it is a post hoc analysis of a randomized trial, so the findings should be interpreted as exploratory. Second, the relatively small number of patients included in this subanalysis limited the number of variables that could be included in multivariable models. Third, information about the location

of coronary restenosis was not available in 14% of the patients who underwent TLR. Fourth, routine angiographic follow-up was not part of the EBC MAIN protocol, nonetheless performing repeat angiograms based on patient symptoms and ischemia testing is more representative of real life clinical practice, that is, clinically driven revascularisation. Finally, use of intracoronary imaging was not mandated and was undertaken in only 40% of patients during the index procedure. This study was not principally concerned with intravascular imaging, hence criteria for optimal stent deployment were not recorded after performing intravascular ultrasound/optical coherence tomograph. Information about intracoronary imaging use was also not available when TLR was performed with PCI during follow-up. Increasing evidence supports the use of intracoronary imaging for PCI of LM true bifurcation lesions, therefore it is likely that outcomes could have been improved if intracoronary imaging was used routinely. It is unclear if adequate stent optimization was achieved in all patients in this study, therefore the absence of an association between stent technique and TLR in this study is not definitive.

## CONCLUSIONS

Three years after contemporary LM bifurcation PCI, the Cx ostium is the commonest location for restenosis requiring revascularization, irrespective of whether dual-or single-stenting was performed. Strategies to improve long-term PCI success within the Cx artery ostium are required.

#### ARTICLE INFORMATION

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#### Supplemental Material

Supplemental Methods Tables S1-S7 Figure S1

#### **REFERENCES**

- Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, Kandzari DE, Karmpailotis D, Brown WM 3rd, Lembo NJ, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med. 2019;381:1820–1830. doi: 10.1056/NEJMoa1909406
- Arunothayaraj S, Egred M, Banning AP, Brunel P, Ferenc M, Hovasse T, Wlodarczak A, Pan M, Schmitz T, Silvestri M, et al. Stepwise provisional versus systematic dual-stent strategies for treatment of true left main coronary bifurcation lesions. *Circulation*. 2025;151:612–622. doi: 10.1161/CIRCULATIONAHA.124.071153
- Takagi K, Ielasi A, Shannon J, Latib A, Godino C, Davidavicius G, Mussardo M, Farrarello S, Figini F, Carlino M, et al. Clinical and procedural predictors of suboptimal outcome after the treatment of drug-eluting stent restenosis in the unprotected distal left main stem: the Milan and New-Tokyo (MITO) registry. Circ Cardiovasc Interv. 2012;5:491. doi: 10.1161/CIRCINTERVENTIONS.111.964874
- Price MJ, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol.* 2006;47:871–877. doi: 10.1016/j.jacc.2005.12.015
- Takagi K, lelasi A, Basavarajaiah S, Chieffo A, Shannon J, Godino C, Hasegawa T, Naganuma T, Fujimo Y, Latib A, et al. The impact of main branch restenosis on long term mortality following drug-eluting stent implantation in patients with de novo unprotected distal left main bifurcation coronary lesions: the Milan and New-Tokyo (MITO) registry. *Catheter Cardio*vasc Interv. 2014;84:341–348. doi: 10.1002/ccd.25178
- Kang SJ, Ahn JM, Song H, Kim WJ, Lee JY, Park DW, Yun SC, Lee SW, Kim YH, Lee CW, et al. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv.* 2011;4:562–569. doi: 10.1161/CIRCINTERVENTIONS.111.964643
- Gil R.J., Bil J., Kern A, Inigo-Garcia LA, Formuszewicz R, Dobrzycki S, Vassilev D, Mehran R. Angiographic restenosis in coronary bifurcations treatment with regular drug eluting stents and dedicated bifurcation drug-eluting BiOSS stents: analysis based on randomized POLBOS I and POLBOS II studies. Cardiovasc Ther. 2020;2020:6760205. doi: 10.1155/2020/6760205
- 8. Hildick-Smith D, Egred M, Banning A, Brunel P, Ferenc M, Hovasse T, Wlodarczak A, Pan M, Schmitz T, Silvestri M, et al. The European bifurcation club left main coronary stent study: a randomized comparison of stepwise

- provisional vs. systematic dual stenting strategies (EBC MAIN). Eur Heart J. 2021;42:3829–3839. doi: 10.1093/eurheartj/ehab283
- Murphy JL, Patel N, Vengrenyuk Y, Okamoto N, Barman N, Sweeny J, Kapur V, Hasan C, Krishnan P, Vijay P, et al. Cardiovascular outcomes after percutaneous coronary intervention on bifurcation lesions with moderate to severe coronary calcium: a single-center registry study. *Catheter Cardiovasc Interv.* 2021;98:35–42. doi: 10.1002/ccd.29069
- Park TK, Lee JH, Song YB, Jeong JO, Hahn JY, Yang JH, Choi SH, Choi JH, Lee SH, Jeong MH, et al. Impact of non-compliant balloons on long-term clinical outcomes in coronary bifurcation lesions: results from the COBIS (COronary Blfurcation Stent) II registry. *EuroIntervention*. 2016;12:456– 464. doi: 10.4244/EIJV12I4A79
- Takagi K, Naganuma T, Chieffo A, Fujino Y, Latib A, Tahara S, Ishiguro H, Montorfano M, Carlino M, Kawamoto H, et al. Comparison between 1- and 2- stent strategies in unprotected distal left main disease: the Milan and New-Tokyo registry. *Circ Cardiovasc Interv.* 2016;9:e003359. doi: 10.1161/CIRCINTERVENTIONS.116.003359
- Espejo-Paeres C, Vedia O, Wang L, Hennessey B, Mejia-Renteria H, McInerney A, Nombela-Franco L, Nunez-Gil IJ, Macaya-Ten F, Salinas P, et al. Propensity-matched analysis of long-term clinical results after ostial circumflex revascularisation. *Heart.* 2023;109:1302–1309. doi: 10.1136/heartjnl-2022-322204
- Lee JY, Park DW, Kim YH, Yun SC, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Incidence, predictors, treatment, and long-term prognosis of patients with restenosis after drug-eluting stent implantation for unprotected left main coronary artery disease. J Am Coll Cardiol. 2011;57:1349– 1358. doi: 10.1016/j.jacc.2010.10.041
- Naganuma T, Chieffo A, Basavarajaiah S, Takagi K, Costopoulos C, Latib A, Carlino M, Montorfano M, Bernelli C, Nakamura S, et al. Single-stent crossover technique from distal unprotected left main coronary artery to the left circumflex artery. Catheter Cardiovasc Interv. 2013;82:757–764. doi: 10.1002/ccd.24988
- Wang Z, Yang J, Li C, Huang J, Fezzi S, Chen E, Cai W, Stankovic G, Wijns W, Chen L, et al. Dynamic assessment of the left main-left circumflex bending angle: implications for ostial left circumflex artery in-stent restenosis after successful two-stent PCI. Int J Cardiol. 2023;378:11–19. doi: 10.1016/j.ijicard.2023.02.030
- Ino Y, Toyoda Y, Tanaka A, Ishii S, Kusuyama Y, Kubo T, Takarada S, Kitabata H, Tanimotot T, Mizukoshi M, et al. Predictors and prognosis of stent fracture after sirolimus-eluting stent implantation. *Circ J.* 2009;73:2036–2041. doi: 10.1253/circj.cj-09-0343
- Gyongyosi M, Yang P, Khorsand A, Glogar D. Longitudinal straightening effect of stents is an additional predictor for major adverse cardiac events. Austrian Wiktor Stent Study Group and European Paragon Stent Investigators. *J Am Coll Cardiol.* 2000;35:1580–1589. doi: 10.1016/s0735-1097(00)00570-2
- Wentzel JJ, Whelan DM, van der Giessen WJ, van Beusekom HM, Andhyiswara I, Serruys PW, Slager CJ, Krams R. Coronary stent implantation changes 3-D vessel geometry and 3-D shear stress distribution. J Biomech. 2000;33:1287–1295. doi: 10.1016/s0021-9290(00)00066-x
- Minami Y, Ong DS, Uemura S, Wang Z, Aguirre AD, Mukhopadhyay S, Soeda T, Vergallo R, Jia H, Tian J, et al. Impacts of lesion angle on incidence and distribution of acute vessel wall injuries and strut malapposition after drug-eluting stent implantation assessed by optical coherence tomography. Eur Heart J Cardiovasc Imaging. 2015;16:1390–1398. doi: 10.1093/ehici/jev108
- Hirohata A, Shiomi T, Yoshioka R. Stentless treatment strategy for left circumflex artery ostial stenosis: directional coronary atherectomy followed by drug-eluting balloon. *J Cardiol Cases*. 2020;21:85–88. doi: 10.1016/j.jccase.2019.10.007
- Chen X, Li X, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, Santoso T, Paiboon C, Kwan TW, et al; DKCRUSH-V Investigators. 3-Year outcomes of the DKCRUSH-V trial comparing DK crush with provisional stenting for left main bifurcation lesions. *JACC Cardiovasc Interv.* 2019;12:1927–1937. doi: 10.1016/j.jcin.2019.04.056
- 22. Chen SL, Sheiban I, Xu B, Jepson N, Paiboon C, Zhang JJ, Ye F, Sansoto T, Kwan TW, Lee M, et al. Impact of the complexity of bifurcation lesions treated with drug-eluting stents: the DEFINITION study (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents). *JACC Cardiovasc Interv.* 2014;7:1266–1276. doi: 10.1016/j.jcin.2014.04.026