REVIEW

Percutaneous coronary intervention to treat unprotected left main: Common (un-answered) challenges

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ABSTRACT

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is a widely adopted strategy to obtain myocardial revascularization in patients with unprotected left main (LM) disease. Although thoroughly investigated across scientific literature, LM PCI offers patient-specific technical options and poses many operative challenges that cannot be fully addressed by the published studies. Therefore, we have summarized and discussed in this review possible options related to PCI in LM patients. First, functional and imaging assessment for LM is still evolving and requires increased dedication to identify patients requiring revascularization and to enhance the results in the case of PCI performance. Second, specific coronary atherosclerosis patterns of LM involvement (like an isolated ostial disease of one of its bifurcation branches, extensive disease jeopardizing both branches, etc.) pose specific challenges for DES implantation so that careful selection of technical options (stepwise provisional single stent, upfront 2-stent strategy, when and how apply "kissing ballooning") is required. Third, despite improvement of techniques, PCI-related ischemia might not be tolerated by some patients with LM disease so mechanical circulatory support devices may come into play.

Key words: left main bifurcation, PCI, ostial disease, and stenting techniques

INTRODUCTION

To date, unprotected left main (LM) percutaneous coronary intervention (PCI) is strongly recommended only in patients with a low (≤22) Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score (class I recommendation) [1]. Yet, progress in PCI techniques is continuously ongoing and, in real-world practice, PCI is offered to many LM patients with a wide spectrum of anatomic complexities. Many specific issues related to LM PCI are not standardized and are heterogeneously approached by different centers and operators. In this paper, we discuss the main unanswered questions that pose challenges in the everyday clinical practice of PCI in patients with ULM.

WHAT ROLE SHOULD FUNCTIONAL AND IMAGING PLAY IN THE ASSESSMENT IN LM DISEASE

According to the current guidelines for myocardial revascularization, angiographic LM stenosis with a cut-off value of ≥50% should be scheduled for revascularization [1]. However, two-dimensional coronary angiography often poorly correlates with actual anatomic (morphological) and functional status [2, 3]. Therefore, supporting imaging and functional assessment in LM treatment should be done more frequently than in any other coronary bed, also due to the amount of supplied myocardium by LM. Various forms of clinical presentation may be crucial in selecting one or both of them. While imaging techniques can

be applied in both chronic and acute coronary syndromes, a functional assessment is mainly oriented to chronic coronary syndrome.

When facing problems in the assessment of LM stenosis significance by angiography, functional evaluation with hyperemic or non-hyperemic tests [4] aims to find eligible patients for safe PCI deferral. Thus, in patients with chronic coronary syndrome (CCS), a fractional flow reserve (FFR) value of >0.8 and instantaneous wave-free ratio (iFR) value of >0.89 are considered to be cut-off values for safe revascularization deferral [5–7]. The same FFR cut-off value could be also used in the estimation of LM severity in patients with NSTEMI [8], while ST elevated acute coronary syndrome should be the reason not to perform a functional assessment. When performing FFR, it is important to highlight that equalization of guiding catheter and wire pressures should be done with a disengaged guiding catheter and that adenosine should be administered as a continuous intravenous infusion with a disengaged guiding catheter throughout all measurements [5]. Furthermore, estimation of LM significance should be done by measuring FFR towards both, left anterior descending (LAD) and left circumflex (LCX), given that FFR or iFR values could be confounded by the concomitant presence of downstream disease, especially LAD [5]. Except to evaluate LM significance, functional assessment tools can be used to navigate intervention and valuate final results [9].

On the other hand, intravascular imaging techniques can be used not only for the assessment of stenosis significance but also for morphological plaque evaluation, particularly in the setting of acute coronary syndrome, and for PCI result optimization as well.

Intravascular ultrasound (IVUS) is used for evaluation of complete LM, from the ostium, across the trunk, and toward distal LM bifurcation, having class IIa recommendation for use in LM PCI [1]. According to IVUS measurement of the LM minimal lumen area (MLA), revascularization may be safely deferred if MLA is >6 mm^2 while treatment is recommended if MLA is <4.5 mm^2 [6, 10]. Of course, MLA may differ and should be tailored by ethnicity and body mass index [11]. A recently published study of IVUS guidance in LM PCI provides prognostic benefits concerning angiography guidance, particularly when following a detailed protocol with predefined optimization criteria (stent expansion and apposition, proximal stent deformation, plaque burden, and dissection at stent edges) [12].

Optical coherence tomography (OCT) as a junior imaging technique has higher axial resolution compared to IVUS, allowing higher image quality and plaque morphology assessment, better distinguishing fine details including residual thrombus, minor edge dissections, and tissue prolapse, which usually have a benign course [13, 14]. Due to the inability to achieve complete blood clearance even with a disengaged guiding catheter and reduced penetration rate, accurate vessel sizing could be limited, thus OCT is discouraged in ostial LM disease. Conversely, OCT assessment is feasible in distal LM lesions [15]. A small study recently reported the feasibility of OCT guidance to support the decision to defer revascularization in low-risk patients with angiographically-intermediate distal LM lesions [16]. Notably, despite the adoption of very conservative OCT parameters prompting revascularization, very few events occurred in deferred patients.

When moving from lesion assessment to PCI optimization, OCT potential is increasingly recognized. Due to the ability of 3D reconstruction, OCT has an advantage in the visualization of struts hanging over the side branch ostium, in the estimation of wire position and wire recrossing point. OCT is accepted as a feasible and safe imaging tool in the distal LM PCI setting, particularly for the detection and correction of acute stent underexpansion and malapposition [17]. The recently published LEft Main Oct-guided iNterventions (LEMON) study, showed that OCT-derived information regarding stent optimization changed procedural strategy in 26% of the studied LM PCI patients [18]. Furthermore, a large retrospective multicenter study comparing OCT with IVUS and angiography in patients who underwent distal LM stenting allowed researchers to document that intravascular imaging was superior to angiography for distal LM stenting, with no difference between OCT and IVUS [19].

Figures 1 and 2 describes the main features of LM functional and imaging assessment.

HOW TO MANAGE ISOLATED OSTIAL LEFT ANTERIOR OR LEFT CIRCUMFLEX ARTERY DISEASE?

One of the most challenging atherosclerotic plaque distribution patterns in LMB is certainly ostial disease of one of its branches. Although described and defined as apparently simple Medina 0.1.0 or Medina 0.0.1 by angiography, the involvement of distal LM disease in these circumstances is often not easy to estimate. According to an IVUS study, isolated ostial LAD and ostial LCX disease were far less common than when appreciated by simple angiography [20]. Similar observations have been collected more recently by OCT [15]. In other words, any time isolated LAD or LCX stenosis is encountered, the main concern to guide therapy is related to the proper assessment of distal LM anatomy.

Concerning the stenting technique, the common choice is between the ostial branch stenting and crossover stenting from LM to the diseased branch (according to either provisional or inverted provisional).

Ostial stenting can pose difficulties with stent positioning, which can lead to the longitudinal geographical miss. If positioned too distal, there is a concern of missing the diseased ostium, and if placed too proximal, it can produce free-floating struts in front of the side branch (SB) ostium, inducing a higher risk for thrombosis and restenosis.

Furthermore, even when properly done, "nailing" the LAD ostium can cause damage to LCX ostium, mostly by shifting/displacement of the carina although the snow-

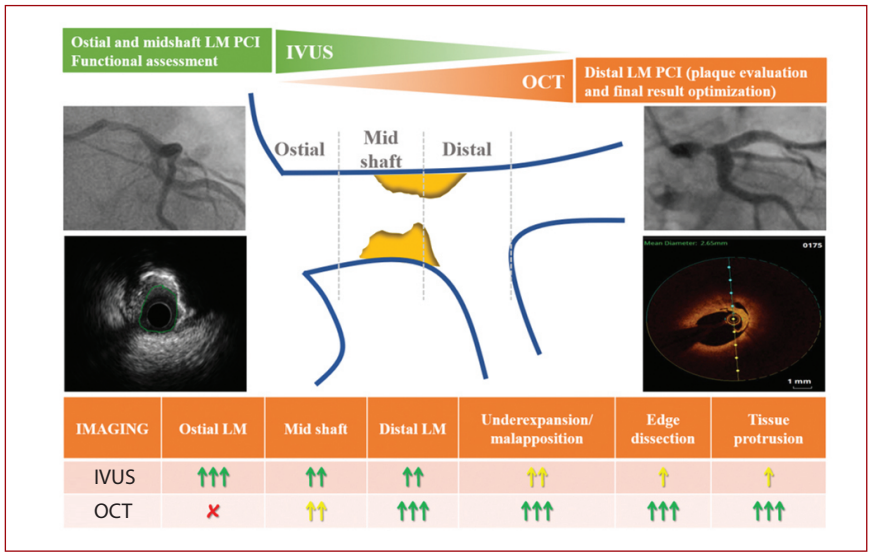
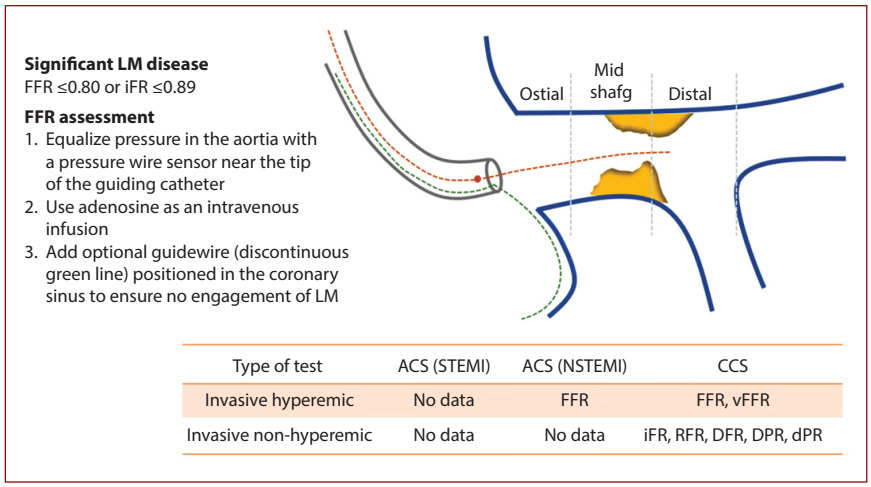


Figure 1. The main features of the left main imaging assessment

Abbreviations: IVUS, intravascular ultrasound; LM, left main; OCT, optical coherence tomography; PCI, percutaneous coronary intervention



Type of test	ACS (STEMI)	ACS (NSTEMI)	CCS
Invasive hyperemic	No data	FFR	FFR, vFFR
Invasive non-hyperemic	No data	No data	iFR, RFR, DFR, DPR, dPR

Figure 2. The main features of the left main functional assessment

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; other — see Figure 1

plow phenomenon (plaque shifting), spasm, and dissection could be seen as well. According to Medina et al. [21], among all features, the presence of the vulnerable carina, spiky carina, morphology described as an "eyebrow" sign on IVUS, was recognized as the only independent predictor of the LCX damage after ostial LAD stenting. Unexpectedly, although the mean stent protrusion in front of the LCX ostium was 2.48 mm (2.8 mm in the group with LCX damage and 2.3 mm in the group without LCX damage), it was not recognized as an independent predictor of LCX damage [21].

However, if the longitudinal geographical miss is recognized, it can be solved either by crossover stenting or with a 2-stent technique, depending on the level and the degree of longitudinal geographical miss. Otherwise, when not recognized immediately, it can cause obliteration of LCX ostium due to fenestrated restenosis. Converting to the 2-stent technique seems to be the best solution as it is shown in Figure 3.

The prevalence of vulnerable carina or "eyebrow" sign is described to be higher in bifurcation lesions with smaller bifurcation angles (LAD-D for example), compared to LMB [22]. Not only in ostial LAD stenting but also in crossover bifurcation stenting, the presence of the "eyebrow" sign is a powerful predictor of SB damage [22].

When all the prerequisites for ostial stenting are met, including proper distal guidewire position and guiding catheter engagement, 3 additional techniques can help to avoid the longitudinal geographical miss.

One of them is the very well-known Szabo technique [23], which was used for aorto-ostial lesions at first and then modified to use for ostial bifurcation lesion stenting. This technique requires a second anchor guidewire which will pass through the last proximal stent strut. The stent is

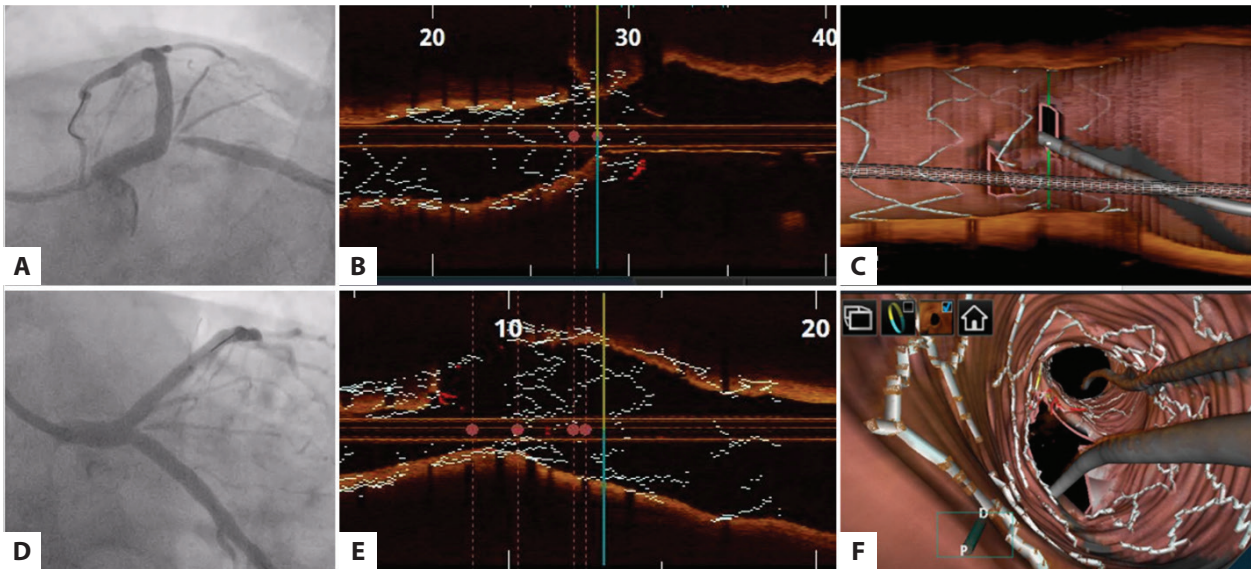


Figure 3. Tight ostial LCX stenosis caused by fenestrated restenosis after ostial LAD stenting with stent struts protruding into the LM. Successful treatment with the mini-Culotte technique. **A.** Ostial LCX stenosis after ostial LAD stenting; **B.** OCT run from LAD showing stent struts protruding into the LM in front of LCX ostium; **C.** Fenestrated restenosis at the LCX ostium; **D.** Final angiography result after PCI (DES 4.0 × 28 mm from LM toward the LCX-mini Culotte technique with a previously implanted stent in LAD); **E–F.** Final OCT run from LAD, showing good stent apposition, short stent overlap in LM (mini Culotte), widely open both SBs and centered carina

Abbreviations: DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; SB, side branch; other — see Figure 1

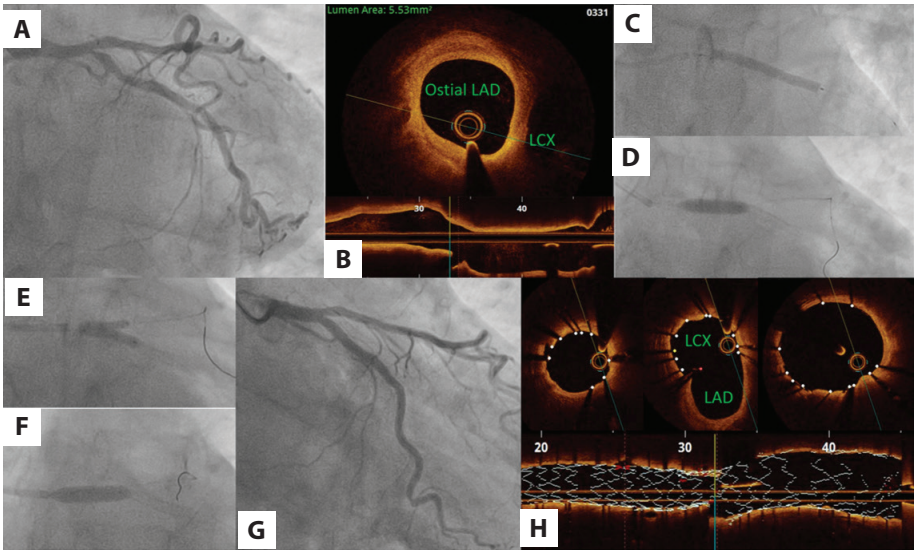


Figure 4. Crossover stenting in isolated ostial LCX disease. **A.** LM bifurcation Medina 0.0.1 (AP-CAU view); **B.** OCT run from LAD before PCI showing tight lesion at the level of LCX and no significant stenosis of ostial LAD and distal LM; **C.** Crossover stenting (DES 3.5 × 38 mm) from LM toward LCX (AP-CRA view); **D.** POT with 4.5 × 12 mm (AP-CAU view); **E.** Kissing with NC balloons 3.25 × 15 mm (LCX) and 2.75 × 12 mm (LAD) balloons; **F.** Repeated POT with 4.5 × 12 mm; **G.** Final angiography result (AP-CAU view); **H.** Final OCT run showing widely open SB (LAD) and perfect stent apposition in LCX and LM

Abbreviations: POT, proximal optimization technique; other — see Figures 1 and 3

advanced over both the primary and the anchor guidewire which is placed in the SB and used to stop the advancement of the stent just at the ostium of the target vessel.

When high mobility of the stent is noticed (due to bobbing or to-and-fro motion of the stent caused by cardiac contraction), other alternatives like the buddy balloon technique [24] or rapid transcoronary pacing [25] have been proposed to increase the chance to deliver the stent in the appropriate location.

In conclusion, despite experience and tricks, precise ostial stenting (notwithstanding its apparent simplicity) should be regarded as a technique associated with a good final result that is difficult to achieve. Accordingly, crossover stenting is often adopted not only in ostial LAD but also in ostial LCX disease as it is shown in Figure 4. According to a small study comparing ostial versus crossover stenting in ostial LAD disease, crossover stenting was associated with numerically lower MACE rates (10.1 vs. 21%; $P = 0.2$) and target vessel revascularization (TVR) rates (5.6% vs. 21%; $P = 0.04$) in comparison to ostial stenting [26]. Another retrospective study confirmed those results and showed that PCI strategy (ostial stenting) was an independent predictor of 1-year MACE (HR 2.561; 95% CI, 1.041–6.299; $P = 0.021$) [27].

Figure 5 summarizes the options to be considered for ostial LAD and LCX treatment.

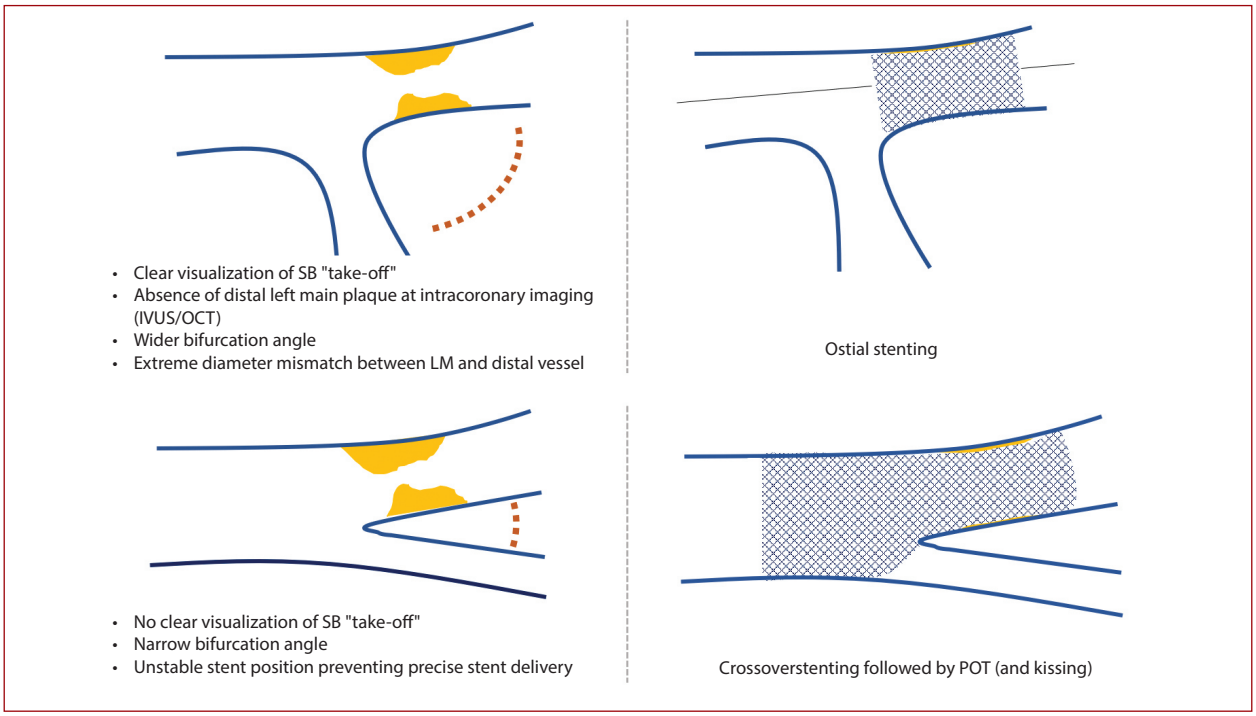


Figure 5. Ostial side branch disease — choosing between ostial versus crossover stenting
Abbreviations: see Figures 1, 3 and 4

WHEN TREATING LEFT MAIN WITH A SINGLE STENT, IS "KISSING" MANDATORY?

The most commonly adopted technique in LM stenting is the stepwise provisional single stent technique. According to this approach, recommended by the European Bifurcation Club (EBC) [28], a stent is implanted in the main vessel (with the size selected according to the distal reference) and appropriate postdilation of the proximal stent segment (lying in the left main) is done with a properly sized balloon according to the proximal optimization technique (POT) technique. These simple steps might imply some challenges in the specific setting of LM where differences in the size of proximal and distal references might be major (so that the stent expansion limits might be reached) and balloons needed might be large (beyond 5 mm). If properly done, with a balloon positioned exactly at the level of the carina, reaching, but not exceeding the proximal stent edge in the absence of ostial coverage [29], POT is known to expand the stent's side cells so that further interventions (like wire and balloon advancement) on the side branch are facilitated. For instance, such partial removal of stent struts from the side branch ostium is sometimes so effective (Figure 6) that the question about the real need to dilate the side branch in the presence of good angiographic results does exist.

While kissing balloon inflation (KBI) is considered to be an obligatory step in the 2-stent strategy, in the provisional single stent strategy, there is conflicting evidence about its usefulness, not only in non-LM but also in LMB (Table 1). Although it is shown that KBI can reduce the incidence of SB restenosis, it does not influence clinical outcomes and is not recommended to be used systematically [30, 31]. Furthermore, the benefit of KBI in terms of MACE reduction has not been confirmed in the recently published sub-analysis of the EXCEL trial [32] investigating the influence of final KBI in the distal LMB.

Notably, there is some evidence that only POT can be considered a protective factor for TLF while both KBI and the joint action of POT and KBI do not affect TLF reduction [34]. However, the lack of randomized trials that investigate the synergism of POT and KBI, as well as a low rate of POT and not reported rate of POT in a majority of trials, may influence the heterogenicity of results (Table 1).

Importantly, although the advantages of systematic KBI in provisional single stenting are not recognized, there was no penalty in the clinical outcome either (Table 1).

However, not only kissing but also the quality of kissing might influence its efficacy and SB opening [35]. More recently, a large registry on ULM PCI with last-generation stents looking at the technique for KBI showed that only short overlap KBI (<3 mm) was associated with a lower rate of target lesion revascularization compared with no KBI (2.6% vs. 5.4%; $P = 0.034$), while long overlap was not (6.8% vs. 5.4%; $P = 0.567$) [36].

Longer proximal balloons overlap, and the use of SC balloons can cause overstretching of proximal MB that becomes oval, which should be fixed with repeated POT. With this re-POT, we aim to restore the round shape of proximal MB, to achieve better stent expansion, to fix malapposition and a "bottleneck" effect if present, thus regaining the fractal geometry of LM [37].

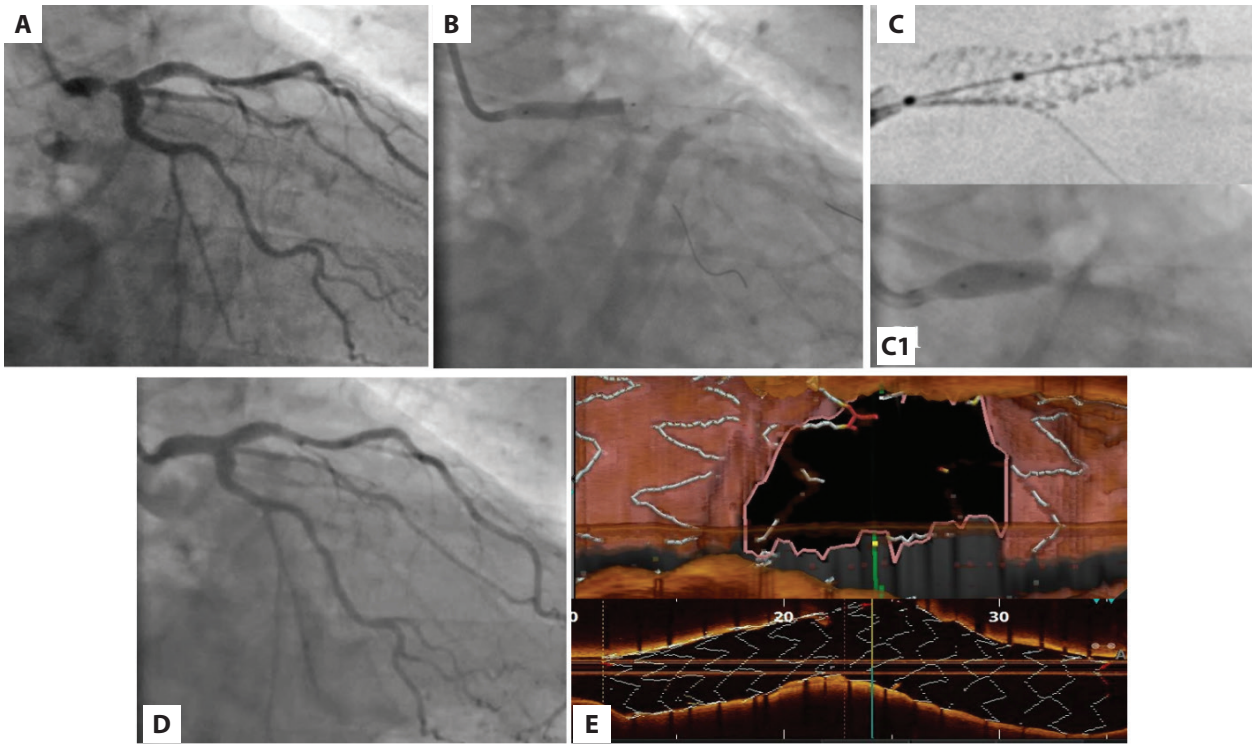


Figure 6. Feasibility of SB opening with properly done POT after crossover stenting in distal LM (Medina 1.1.0). **A.** LMB Medina 1.1.0; **B.** Implantation of DES 4.0 × 24 mm in LM-LAD; **C.** Stent boost for precise POT balloon positioning; **C1.** POT with NC balloon 5.0 × 15 mm; **D.** Final angiography result; **E.** Final OCT showing wide SB opening (upper picture) and perfect adaptation of the stent of the 2 diameters of LM and LAD (bottom picture)

Abbreviations: see Figures 1, 3, 4

Table 1. Effect of KBI vs. no KBI in provisional single stent technique in the trials that included LMB

Study/first author	Study design	No. of patients	% LM	KBI (N)	POT (%)	Follow-up, months	% MI KBI vs. no KBI	% Cardiac death KBI vs. no KBI	% TLR KBI vs. no KBI	% MACEb KBI vs. no KBI
COBIS II [61]	Registry	1901	25.9	620	NA	36	0.6 vs. 1.8	0.6 vs. 1.2	5.8 vs. 6.6	6.8 vs. 8.6[a]
NORDIC III [62]	RCT	477	8.0	238	NA	6	0.4 vs. 1.3	0.8 vs. 0.0	1.3 vs. 1.7	2.1 vs. 2.5
AOI-LMCA [63]	Registry	738	100	578[d]	NA	48	2.6 vs. 6.4	6.3 vs. 9.1	10.7 vs. 14.3	17.0 vs. 21.3
SMART-STRATEGY [64]	RCT	258	44.1	130	NA	12	0 vs. 0	0.8 vs. 0.0	5.4 vs. 7.8	9.2 vs. 9.4
CORPAL [65]	RCT	244	8.2	124	31	12	0.8 vs. 0.8	1.6 vs. 0.8	4 vs. 1.7	9.0 vs. 6.0
ASAN-MAIN [66]	Retrospective	413	100	95	NA	24	0 vs. 0.7	4.6 vs. 3.9	8.1 vs. 4.8	12.5 vs. 8.5
Gao [67]	Retrospective	790	100	230	NA	48	5.7 vs. 7.5	3.5 vs. 3.0	3.5 vs. 5.0	7.8 vs. 10
I-BIGIS [68]	Retrospective	2849	13.1	1176	NA	22.4	4.9 vs. 3.4	2.9 vs. 2.7	10.7 vs. 8.9	14.5 vs. 12.7
Hariki [69]	Retrospective	76	7.9	33	NA	25.9	NA	NA	9.1 vs. 12.8	6.1 vs. 2.6
RAIN-CARDIOGROUP VII [36]	Registry	2099	NA[e]	755	NA	16	7.3 vs. 5.3	6.1 vs. 6.6[f]	5.3 vs. 3.2	15 vs. 12.4
EXCEL [32]	RCT	430	100	175	NA	48	8.4 vs. 5.6	4.8 vs. 3.6 10 vs. 9.3[f]	9.5 vs. 9.5	17.5 vs. 15.9[c]
COBIS III [33]	Retrospective	2194	31.1	509[d]	28.7	60	2.4 vs. 1.5	2.8 vs. 3.0	3.5 vs. 4.0	6.7 vs. 7.0
Chevalier et al. [34]	Registry	4180	13.6	1517	37.7	12	1.0 vs. 1.9	1.8 vs. 1.6	2.4 vs. 2.7%	4.5 vs. 4.7

[a]*P* <0.05. [b]MACE-Target lesion failure (defined as a composite of cardiac death, target vessel MI, or target lesion revascularization). [c]Primary endpoint (death, MI, stroke); [d]SB opening; [e]26.7% in the overall RAIN-GROUP VII population that included 2742 patients. [f]All-cause death

Abbreviations: KBI, kissing balloon inflation; LM, left main; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not applicable; POT, proximal optimization technique; RCT, randomized clinical trial; SB, side branch; TLR, target lesion revascularization

Another technique for SB opening in crossover stenting is POT-side-rePOT [38, 39]. This technique consists in single balloon dilatation of SB ostium after the first POT and properly done distal rewiring, followed by repeated POT. Although simple and feasible, with a reduction of SB obstruction from 26% to 3.3% in the experimental model [38], it can distort the stent, usually on the opposite wall, especially if the SB is of a bigger diameter; the larger the balloon, the larger the stent deformation.

However, in LMB, especially in true LMB, with a large amount of jeopardized myocardium in the SB territory, the only acceptable SB opening technique would be kissing, practiced in a refined way, in a joint action of POT, distal SB rewiring, and done with short proximal overlap and followed with re-POT. Only in this way, complete struts clearance in front of SB ostium and relocation of carina in the center can be obtained, thus improving wall shear stress [40].

Nevertheless, when dealing with LM trifurcation disease, which is distinct due to the presence of 2 SBs, 2 carinas, at least four angles, in provisional single stent technique, after essential POT, two-step kissing or triple balloon kissing ("trissing") is advisable for side branches opening and relocation of both carinas [41].

WHICH TECHNIQUE FOR LEFT MAIN BIFURCATION WITH EXTENSIVE DISEASE IN BOTH BRANCHES?

One of the most frequently asked questions in LM PCI, especially in the presence of extensive disease in both branches, defined as true LM bifurcation (Medina 1.1.1, Medina 1.0.1, or Medina 0.1.1), is whether to select upfront the two stent technique or to downgrade it to a single stent technique and in what circumstances.

A recently conducted meta-analysis of nine randomized controlled trials with 3265 patients, evaluating long-term outcomes (≥1 year) according to treatment strategy for coronary bifurcation lesions concluded that provisional single stenting was associated with lower all-cause mortality (2.94% vs. 4.23%; risk ratio: 0.69; 95% CI, 0.48–1.00; $P = 0.049$) [42].

However, when focusing on LM bifurcation lesions only, the first and until recently the only randomized trial conducted in these subgroup of patients, DKCRUSH-V showed superior results with the double kissing (DK) crush technique over the provisional single stent technique [43], therefore DK crush is considered as preferred option to treat true LMB (Class of recommendation IIb, level of evidence B) [1].

On the other hand, the recently published EBC MAIN trial [44] compared the stepwise provisional single stent strategy, which could convert into two stents as a bailout (patients with <TIMI 3 flow in SB, >90% of ostial pinching of SB, threatened SB closure or dissection > type A), with the upfront 2-stent technique in true distal LMB. It showed that there was no difference in the primary composite endpoint at 1 year (14.7% in stepwise provisional single stent vs. 17.7% in the upfront 2 stent group). There was no significant difference in any of the individual components of the primary endpoint.

Comparing those 2 trials (Table 2), the DK CRUSH-V population had a higher mean SYNTAX score in comparison to the EBC MAIN trial (31 vs. 23), with a higher SB lesion length (16 vs 7 mm), which is why almost half of the patients in DK CRUSH-V were converted from a single to 2-stent technique (47.1% of patients). By comparison, in the EBC MAIN trial, only 22 % of patients randomized to a single stent strategy converted to two stent strategy (Culotte or T/TAP equally).

The contradictory results of the ten RCTs evaluating outcomes between 1 versus 2 stents in bifurcation lesions that included LMB (Table 2), may be explained by the diversity of the study population, which not only presented true LMB lesions but also by disease complexity and the extent, presence of calcium, and unfavorable angles which can influence the outcome [45–48], as well as heterogenicity of double stenting techniques.

Furthermore, when it comes to stenting optimization techniques, although there are also conflicting results (Table 3), it is important to underline that unlike in the provisional single stent technique, where kissing is optional, in two stent strategy, it is shown that final KBI can influence outcomes and should be considered mandatory [36]. In the 2-stent subgroup of patients included in the large RAIN-CARDIOGROUP VII registry, final KBI was associated with lower rates of TVR (7.8% vs. 15.9%; $P = 0.030$) and target lesion revascularization (7.3% vs. 15.2%; $P = 0.032$), thus demonstrating the necessity of applying KBI in 2 stent techniques [36]. Importantly, KBI is done in a specific manner (sequential kissing with non-compliant balloons with short proximal overlap [40]).

Consequently, the stepwise provisional single stent strategy may be a reasonable option to treat the majority of true LMB lesions, of course, bearing in mind the complexity and the extent of the disease, discrepancy in SB diameters, and presence of unfavorable angles, which can make operators convert to two stent strategy if needed. Thus, in complex LMB with diffusely diseased, calcified SB and particularly with unfavorable SB take-off, when SB damage could be expected after MB stenting or SB needed to be treated first, we should start with an upfront 2 stent technique. In all other circumstances, and when there is no damage of SB after MB stenting, we should continue with a single stent strategy. However, if the result in SB is not satisfactory (dissection >type A, impaired flow), then proceeding to a 2-stent technique is mandatory (either Culotte or T/TAP, mainly based on bifurcation angle), followed by obligatory sequences of POT, kissing and re-POT.

Table 2. Trials on single stent vs. 2-stents in bifurcation lesions

Study/year	No of pts	1[c] end--point	True bif. % (1 vs. 2 stents)	LMB, %	2-stent technique, %	SB lesion length, mm	SB stenosis diameter % (1 vs. 2 stents)	% of pts with B angle < 70[c] (or avg degree)	Cross--over from 1 to 2 stents, %	KBI 1 vs. 2 stents	Follow--up, years	MI 1 vs. 2 stents, %	Death 1 vs. 2 stents, %	TLR 1 vs. 2 stents, %	Primary end-point 1 vs. 2 stents, %
NORDIC 2013 [70]	413	MACE (CD, NPMI, TVR, ST)	72 (77 vs. 67)[a]	0.7	Crush (50) Culotte (21) Other (29)	5	NA	63 vs. 66	4.4	32 vs. 74	5	4.0 vs. 7.9	5.9 vs. 10.4	11.3 vs. 15.3	15.1 vs. 21.8
BBK 1 2015 [71, 72]	202	All-cause de-ath, MI or TLR	68.3	0	T stent	10.2	53.8	(49.9 vs. 47.6)	18.8	100 vs. 100	5	NA	7.9 vs. 10.0	16.2 vs. 16.3	22.8 vs. 22.9
PERFECT 2015 [73]	419	CD, MI or TVR	86.6	0	Crush (99)	9.3	55.2	NA	28.2	79 vs. 96	1	14.1 vs. 14.1	1.0 vs. 1.4	3.4 vs. 1.9	18.5 vs. 17.8
NORDIC BALTIC Bifurcation IV 2015 [74]	446	MACE (CD, NPMI, TLR and def ST)	100	2	Culotte (67) T-stent (7) Other (26)	5.8	45.8	49.3 vs. 48.9	3.7	36.1 vs 91.2	2	5.1 vs. 3.1	2.3 vs. 2.2	9.2 vs. 6.2	12.8 vs. 8.4
BBC1 2016 [75, 76]	500	Death	83.2 (81 vs. 84)	0	Crush (68) Culotte (30) Other (2)	NA	NA	85 vs. 87[d]	2.8	29 vsc 76	5	3.6 vsc 11.2[a]	0.4 vsc 0.8	5.6 vsc 7.2[e]	8.0 vs 15.2[a]
EBC TWO 2016 [77]	202	Death, MI or TVR	100	0	Culotte	10.3	54.5	NA	16	94 vs. 96	1	4.9 vs. 10.3	2.0 vs. 1.1	2.9 vs. 1.0[f]	7.7 vs. 10.3
SMART STRATEGY 2016 [78]	258	TVF (CD, spont. MI or TVR)	66.3	44.2	TAP	NA	NA	NA	7	26 vs. 69	3	0 vs. 3.1	0.8 vs. 3.1[b]	8.6 vs. 11.5	11.7 vs. 20.8[a]
DK CRUSH II 2017 [79]	370	CD, MI or TVR	100	16.7	DK Crush	15	NA	NA	29	79.2 vs. 100	5	3.2 vs. 3.8	3.2 vs. 2.2[b]	16.2 vs. 8.6[a]	23.8 vs. 15.7
DK CRUSH-V 2017 [43]	482	CD, TVMI, or TLR	100	100	DK Crush	16	65.6 (65.3 vs. 65.8)	(79.7 vs. 76.3)	47.1	78.9 vs. 99.6[a]	1	2.9 vs. 0.4[a,c]	2.1 vs. 1.2[b]	7.9 vs. 3.8	10.7 vs. 5.0[a]
EBC MAIN 2021 [44]	467	Death MI TLR	100	100	Culotte (53) T/TAP (32) DK crush (5)	7	53.6 (51.9 vs. 55.4)	(80.4 vs. 82.3)	22	89 vs. 93	1	10 vs. 10.1	3.0 vs. 4.2	6.1 vs. 9.3	14.7 vs. 17.7

[a]*P* <0.05. [b]Cardiac death. [c]Target vessel MI. [d]Bifurcation angle <60%. [e]Target vessel failure (TVR with PCI or CABG or postprocedural TIMI<3 in either MB or SB). [f]Target vessel revascularization

Abbreviations: CABG, coronary artery bypass grafting; CD, cardiac death; LMB, left main bifurcation; NPMI, non-procedural MI; ST, stent thrombosis; TVMI, target vessel MI; TVR, target vessel revascularization; other — see Table 1

Table 3. Effect of KBI vs. no KBI in the 2-stent technique in the studies that included the left main bifurcation

Study/first author	Study design	Number of patients	% left main	KBI, n	POT, %	Follow-up months	% MI KBI vs. no KBI	%Cardiac death KBI vs. no KBI	% TLR KBI vs. no KBI	% MACE KBI vs. no KBI
Ge et al. [80]	Observational	181	26.5	116	NA	9	10.3 vs. 13.9	1.7 vs. 0.0	9.5 vs. 24.6[a]	19.8 vs. 38.5[a,d]
Grundeken et al. [81]	Registry	745	5.6	624	NA	6	5.0 vs 4.6	1.7 vs 4.6[a]	4.7 vs 2.9	9.2 vs 10.1[e]
RAIN-CARDIOGROUP VII [36]	Registry	439	NA[b]	321	NA	16	vs 6.0	6.6 vs. 3.9[c]	7.3 vs 15.2[a]	16.6 vs 24.9[f]
EXCELsubstudy [32]	Substudy from RCT	329	100	235	NA	48	13.5 vs 14.4	7.4 vs 10 8.6 vs. 17.4[a,c]	17.3 vs 14.1	19.8 vs 25.8[g]

[a]*P* <0.05. [b]26.7% in the overall RAIN-GROUP VII population that included 2742 patients. [c]All-cause death. [d]MACE-cardiac death, MI and TVR. [e]Target vessel failure (TVF) — cardiac death, any MI and TVR; [f]MACE — all-cause death, MI, TLR, and stent thrombosis. [g]MACE — death, MI, or stroke

Abbreviations: see Tables 1 and 2

WHAT ABOUT HEMODYNAMIC STABILITY DURING LM PCI?

One of the most challenging situations in terms of possible hemodynamic compromise and poor clinical outcome is, for sure, LM PCI in the setting of absent right coronary artery (RCA) support. The definition of absent RCA support varies throughout the published data, with chronic total occlusion (CTO) being the most common. Although the majority of patients with LM disease and RCA CTO are scheduled for coronary artery bypass grafting (CABG) [49], it is not an infrequent situation to deal with LM PCI in this particular setting. The current data support the fact that patients with concomitant RCA CTO have a worse outcome and a higher mortality rate in comparison to patients without RCA CTO [50–52], with RCA CTO as an independent predictor of 3-year cardiac mortality in LM PCI (HR 2.15 [1.02–4.05]; $P = 0.043$) [51]. Furthermore, it is shown that the recanalization of RCA CTO significantly improves long-term survival [52].

Contrary to previous retrospective trials and registries, the recently published data by Skorupski et al. [53] failed to demonstrate the impact of RCA support on prognosis in patients undergoing LM PCI and exhibited a low risk of both acute hemodynamic compromise and late adverse outcome. However, the study population enrolled by Skorupski et al. [53] was characterized by the broad definition of absent RCA support, including patients not only with RCA CTO (only 14.3% of patients) but also with significant stenosis or recessive (non-dominant) RCA. Furthermore, the average SYNTAX score of 21, EuroSCORE II of 1.45%, and preserved ejection fraction (mean value around 55%) definitely influenced the results in this trial.

When faced with significant RCA stenosis in patients selected for LM PCI, it has also been shown that PCI on significant (>70%) RCA stenosis during the same hospitalization might reduce the rate of 30-day cardiovascular death [54].

Altogether, these data imply that the relevance of RCA support is strongly predisposed and influenced by the clinical condition of the patients (acute vs. chronic coronary syndrome), left ventricular ejection fraction, and complexity of LM PCI (Figure 7).

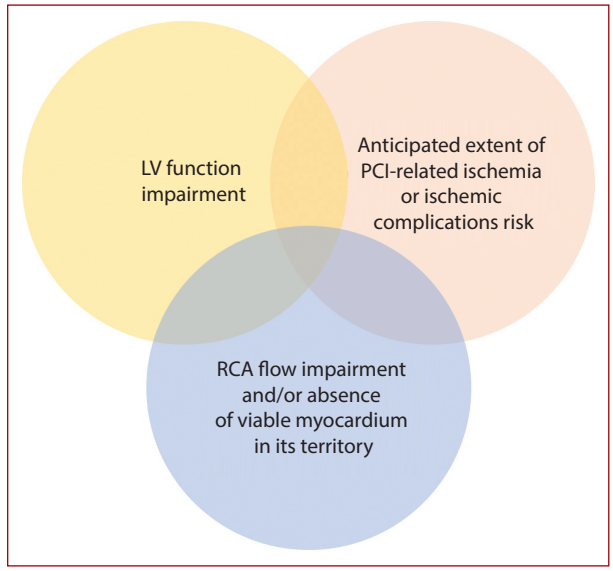


Figure 7. Factors that might be assessed when considering hemodynamic support during left main PCI planning

Abbreviations: LV, left ventricle; RCA, right coronary artery; other — see Figure 1

Thus, in the case of complex LM PCI in the setting of poor/absent RCA support (RCA stenosis or CTO), an individual approach to each patient is recommended. In complex, diffusely diseased LM PCI with reduced EF, which is considered a "high-risk PCI", the use of short-term mechanical circulatory support ("protected" PCI) is advisable to increase procedural safety [55, 56]. Furthermore, in patients with a large area of jeopardized myocardium due to RCA disease (significant stenosis of dominant proximal RCA) undergoing LM PCI, it is recommended not to leave untreated, since it is shown that it may result in impaired late outcome despite successful protected PCI [56, 57]. Despite the conflicting result of the use of MCS in high-risk PCI, except in the prevention of hemodynamic collapse, short-term MCS (preferably "axial flow pump" as Impella,

HeartMate PHP, iVAC2l) should provide adequate time to achieve optimal and complete revascularization (or a reasonable level of revascularization completeness) [58, 59].

CONCLUSIONS

According to the current evidence about the most challenging issues in LM PCI summarized in this review and concerning the amount of myocardium at risk and possible consequences, it is important to highlight several crucial points:

- pragmatic use of functional assessment and imaging techniques in LM evaluation, guidance, and final result assessment;
- if weighing between stenting techniques, the stepwise provisional single stent is preferable over the two stent technique;
- different techniques can be used for SB opening, but POT cannot be omitted;
- in ostial SB disease, do not hesitate to perform crossover stenting.

Concerning all the mentioned above points, it is obvious that LM PCI should be done only by an experienced intervention cardiologist [60] familiar with all bifurcation techniques, intracoronary imaging, and mechanical circulatory support devices.

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