STATE-OF-THE-ART PAPER

Optimizing Outcomes During Left Main Percutaneous Coronary Intervention With Intravascular Ultrasound and Fractional Flow Reserve

The Current State of Evidence

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Percutaneous coronary intervention (PCI) is an evolving indication for the treatment of unprotected left main coronary arterial (UMLCA) stenoses in selected individuals. Intravascular ultrasound (IVUS)-guided PCI within the epicardial coronary tree has been shown to improve acute procedural results and subsequent clinical outcomes. Similarly, fractional flow reserve (FFR) is rapidly gaining popularity as a means to guide the coronary interventionalist to embark upon a "physiological-based" revascularization strategy. In light of the emergence of PCI for ULMCA stenoses, the lack of randomized trials has meant that there are no systematic guidelines that advocate the routine use of these adjunctive imaging techniques to optimize procedural and clinical outcomes. Given the potential dire clinical consequences of procedural failure during ULMCA PCI, in this review we systematically address the current level of evidence for the use of FFR and IVUS during the assessment for and undertaking of PCI for ULMCA stenoses. In lieu of the current available level of evidence, we recommend the use of FFR for the assessment of (angiographic indeterminate) isolated ostial or midshaft left main coronary arterial (LMCA) stenoses in patients who are considered more appropriate candidates for coronary arterial bypass grafting. In those patients with distal/bifurcation LMCA lesions and in those with diffuse/distal coronary arterial disease, we strongly recommend the liberal use of IVUS. Furthermore, in those patients considered likely candidates for ULMCA PCI, IVUS remains crucial for assessing the degree of lumen compromise and the extent, distribution, and morphology of plaque as well as for the immediate postprocedural quantification of stent deployment. (J Am Coll Cardiol Intv 2012;5:697–707) © 2012 by the American College of Cardiology Foundation

Although once considered a relative contraindication and widely discouraged, percutaneous coronary intervention (PCI) for unprotected left main coronary arterial (ULMCA) stenosis is now rapidly emerging as a viable alternative to coronary artery bypass grafting (CABG), long-considered the standard of care for such lesion subsets. Collective data from numerous worldwide registries (1–7) and more recent results from the randomized SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (8) have highlighted PCI for UMLCA as a viable alternative in selected patient groups. Accordingly, PCI for ULMCA stenosis has had an evolving indication, with a recent Class IIa (Level of Evidence: B)

indication within the latest European guidelines (for isolated left main coronary arterial [LMCA] disease or for 1-vessel disease providing the lesion involves the ostium or shaft the LMCA segment) (9), slightly ahead of the Class IIb (Level of Evidence: B) indication stipulated within the current U.S. guidelines (10). The parallel emergence of adjunctive imaging tools (intravascular ultrasound [IVUS], fractional flow reserve [FFR]) has allowed coronary interventionalists to greatly optimize lesion selection and improve immediate procedural and clinical results (11,12), yet the routine uptake of such techniques by the interventional community has been somewhat modest (13). In this review, we highlight the current state of evidence for the use of IVUS and FFR during PCI for ULMCA stenoses.

Assessing the True Severity of LMCA Stenoses: From Structure to Physiology

The dissociation between angiography (or "lumenography"), the true extent of plaque burden, and corresponding physiological significance of coronary arterial stenoses has been well-described (14), none more evident than within the LMCA segment. Initial data revealed significant discrepancies between angiographic estimates of stenosis severity and findings at autopsy (15). This was later documented in vivo with IVUS (16). The uniqueness of the LMCA segment when compared with the epicardial coronary tree ensures that the simple reliance on angiographic assessment of lesion severity might be fraught with inaccuracy. Its short-length, the presence of overlapping daughter branches, the concealment of diffuse atherosclerosis due to arterial remodeling, the distinct lack of a reference segment, and issues of catheter placement and contrast "streaming" for assessing the presence of ostial disease make the accurate assessment of the LMCA segment notoriously difficult even by the most experienced of clinicians (Fig. 1). Furthermore, the LMCA is unique in that it might exhibit reverse tapering, such that the ostium is of smaller caliber than the distal section before the origin of daughter branches, despite the absence of atherosclerosis (17) (Fig. 2). From a clinical standpoint, the difficulty of simply achieving concordance in the agreement of lesion severity was highlighted in a subanalysis of CASS (Coronary Artery Surgery Study), whereby there was only 41% to 59% agreement between experienced angiographers at a clinical site, a quality control site, and those on a study consensus panel (18). From a physiological standpoint, recent studies have highlighted that correct lesion classification by experienced interventional cardiologists occurs in no >50% of occasions, with large interobserver variabilities (19,20).

Using FFR to Guide Decision Making for ULMCA Stenoses

The physiological assessment of epicardial coronary lesions(s) via FFR is now well-validated and established as the invasive "gold-standard" approach in localizing myocardial ischemia, with a greater specificity than comparative non-invasive techniques in localizing myocardial ischemia (21). Since the results of the DEFER (22) and FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) (12) trials, the adoption of an FFR-based PCI strategy has been gaining popularity around the world. Although LMCA disease was an exclusion criteria within the DEFER and FAME trials, FFR has nevertheless been used for evaluation of the physiological significance of indeterminate ULMCA lesions.

Although underpowered to detect meaningful differences between differing patient groups, earlier studies highlighted the potential for FFR to guide decision making with regard to the need for revascularization of isolated, angiographically indeterminate LMCA stenoses (23). Table 1 summarizes the results of these similarly designed trials to date, with a collective enrollment of 449 patients and a mean follow-up period of 29 months (20,24–28). As a whole, these data provides support for the utility of an FFR-based approach to guide decision making for the management of angiographically indeterminate lesions within the LMCA segment.

However, a number of important caveats of this approach warrant further consideration. At present, there is a lack of randomized data from larger multicenter studies confirming the long-term safety of this approach. Also, as to the use of FFR per se, it remains debatable as to whether an FFR <0.75 versus an FFR of <0.80 should be regarded as the appropriate ischemic threshold. Some proponents of the FFR technique to assess LMCA severity suggest the complementary use of IVUS to assess LMCA severity if the LMCA FFR is between 0.80 and 0.85 (29). At least 50% to 60% of ULMCA lesions involve the distal bifurcation, often with significant involvement of the ostia of both daughter branches. Therefore, an FFR pullback should be undertaken starting within both daughter branches to localize the most significant distribution of disease across the region bordering the distal LMCA segment and ostia of both daughter branches. FFR readings across the LMCA segment will be influenced by the presence of lesions within distal coronary
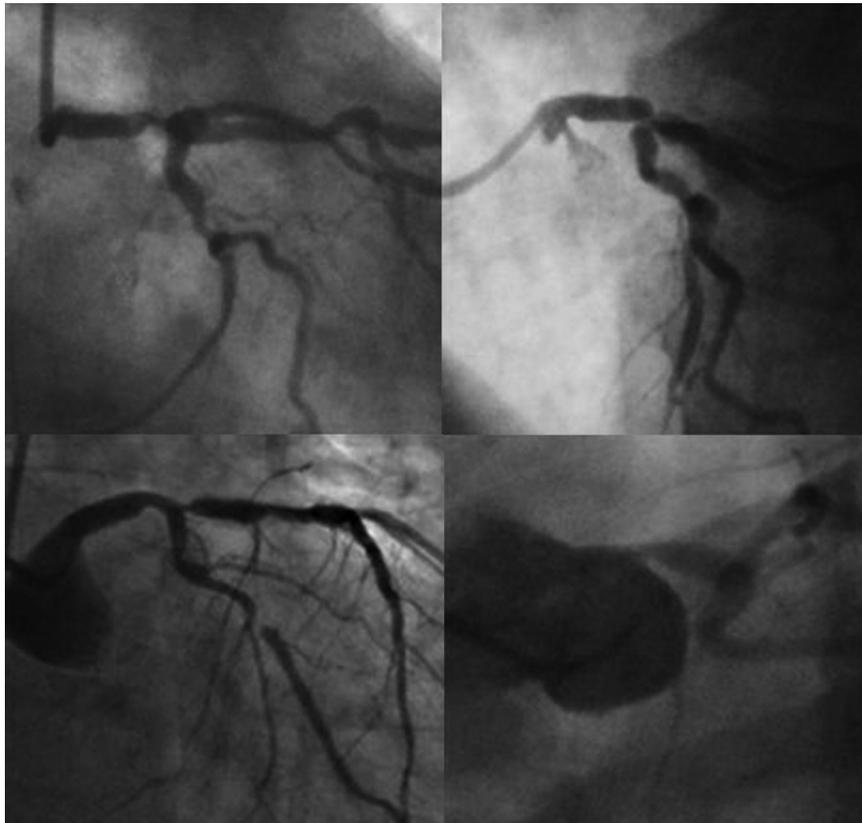
Figure 1. Left Main Coronary Artery

The left main coronary artery comes in all shapes and sizes.

segments as well as the amount of functional myocardial territory supplied by these lesions (Fig. 3). Stenoses within the left anterior descending (LAD) or left circumflex (LCX) territories will artificially increase the FFR measured across the LMCA stenosis (30), and therefore PCI to these lesions would unmask the true hemodynamic significance of the stenosis within the LMCA segment. Recanalization of a stenotic right coronary artery lesion would also modestly increase the FFR across a lesion within the left coronary system (31). Additionally, the inter-individual variation in hyperemic response is varied (32), and higher doses of intravenous adenosine might need to be administered to achieve an optimal response.

Using IVUS to Guide Decision Making for ULMCA Stenoses

Although the correlation of IVUS measurements with FFR findings within the epicardial coronary tree are modest (33–35), the relatively larger size and limited variability of LMCA length have allowed a greater degree of concordance between IVUS and FFR for assessing LMCA lesion significance. Abizaid et al. (36) were the first to report the importance of LMCA lumen dimensions, when IVUS was used to evaluate the prognostic significance of indeterminate LMCA lesions over 1 year. Although no formal minimum LMCA IVUS-derived parameter was defined as a threshold for predicting clinical outcome, the LMCA minimum lumen diameter (MLD) on IVUS was the strongest predictor of the rate of major adverse cardiac events (MACE), whereas the burden of LMCA segment atherosclerosis on IVUS was not found to be predictive of MACE. There was a progressive relationship between the degree of MLD compromise and subsequent MACE rates. Irrespective of the actual LMCA segment MLD measured on IVUS, the presence of coronary stenoses in other vessels and/or diabetes mellitus were strong determinants of 1-year MACE. A subsequent smaller study (37) corroborated the findings of Abizaid et al. An important caveat to note from these studies is that MACE were largely driven by revascularization rates, undertaken at the discretion of the treating clinician.

After this, 2 outcome-based studies were published to address this issue of concordance between IVUS and FFR values in angiographically indeterminate LMCA lesions. Jasti et al. (24) performed sequential FFR and IVUS
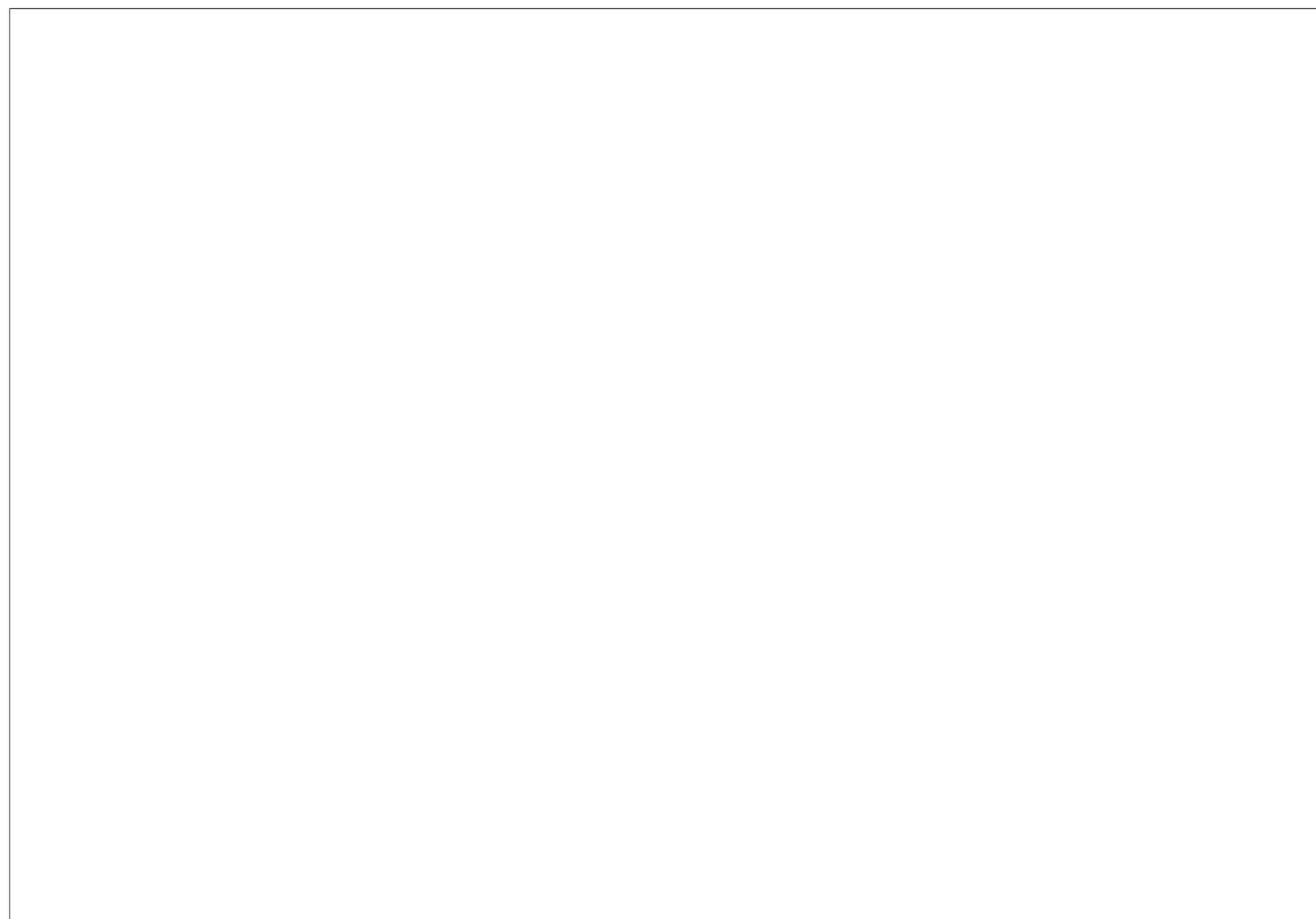
Figure 2. Ostial Stenosis of the LMCA

A and B show the angiographic projections of what seems to be an ostial stenosis of the left main coronary artery (LMCA), despite intracoronary nitroglycerine administration and a patent mammary graft. However, **C** (ostial LMCA) and **D** (distal LMCA) show no significant atherosclerosis and significantly smaller ostial lumen area by intravascular ultrasound. Minimum lumen area by intravascular ultrasound at the left main ostium was 11.4 mm^2 compared with 24.2 mm^2 at the distal left main region.

measurements across angiographically indeterminate LMCA lesions. Compared with the FFR of <0.75 (across the LMCA segment) as being the "gold-standard" measure of functional significance, an MLD of 2.8 mm on IVUS was found to have the highest sensitivity and specificity (93% and 95%, respectively) for identifying the true functional

Table 1. Summary of FFR-Guided Clinical Outcomes Trials Involving Assessment and Treatment Decision Making for ULMCA Stenoses

First Author (Ref. #)	N			FFR Cutoff Value	FU (Months) Mean Duration	Overall Survival	
	Total	Defer Group	Surgical Group			Defer Group (%)	Surgical Group (%)
Bech et al. (23)	54	24	30	0.75	29 ± 15	100	97
Jasti et al. (24)	51	37	14	0.75	25 ± 11	100	100
Jiménez-Navarro et al. (25)	27	20	7	0.75	26 ± 12	100	86
Legutko et al. (26)	38	20	18	0.75	24 ± 12	100	89
Suemaru et al. (27)	15	8	7	0.75	33 ± 10	100	100
Lindstaedt et al. (28)	51	24	27	0.75	29 ± 16	100	81
Hamilos et al. (20)	213	138	75	0.80	35 ± 12	90	85
Total or (mean)	449	271	178	—	(28 ± 13)	(95)*	(89)

*p = NS compared with surgical group.

FFR = fractional flow reserve; FU = duration of follow-up; ULMCA = unprotected left main coronary artery.
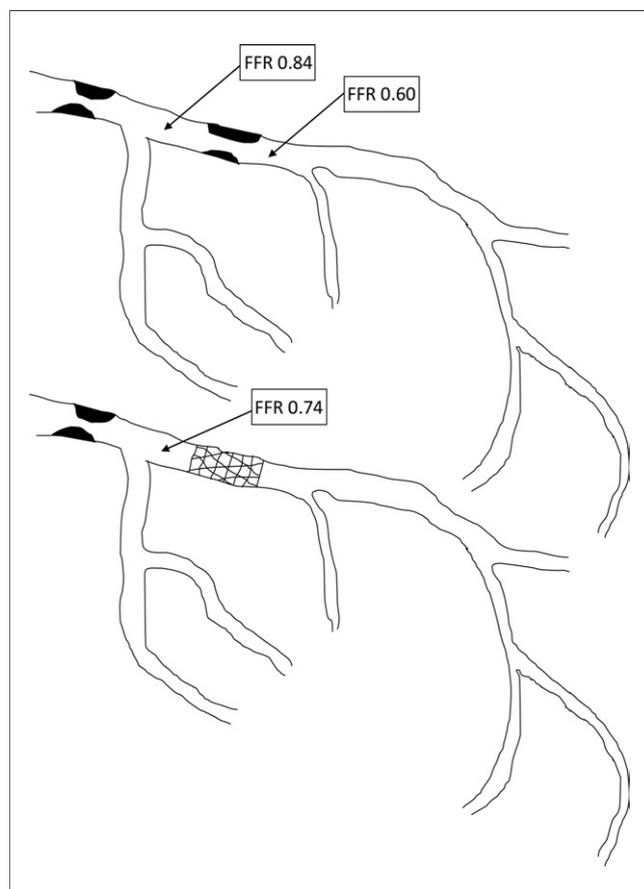
Figure 3. Tandem Lesion Downstream

This type of lesion will mask the true hemodynamic significance of the left main coronary artery lesion by compromising hyperemic flow and subsequent true maximal pressure gradient across this lesion. After percutaneous coronary intervention to the distal lesion, hyperemic blood flow through the vessel has increased, hence the true fractional flow reserve (FFR) of the left main coronary artery lesion becomes apparent.

significance of the ULMCA stenosis. This was followed by minimum lumen area (MLA) on IVUS of 5.9 mm^2 (93% sensitivity, and 95% specificity). Patients with a ULMCA segment FFR <0.75 underwent revascularization of this segment, compared with patients whose ULMCA segment FFR reading was ≥0.75, who remained on medical therapy, unless revascularization of an epicardial coronary lesion was required. The 38-month Kaplan-Meir survival estimates for both FFR groups (<0.75 and ≥0.75) were 100% (p = NS) (24).

More recently, Kang et al. (38) investigated 55 patients with isolated UMLCA stenoses (30% to 80% diameter stenosis severity) that underwent IVUS and FFR before intervention. The only independent predictor of an FFR <0.80 was the LMCA lesion MLA on IVUS (adjusted odds ratio: 0.312, p < 0.001). An MLA on IVUS of <4.8 mm^2 was found to best predict an FFR <0.80 (89% sensitivity, 83% specificity). Greater lesion length on an-

giography was also found to be associated with functional significance. As such, the dynamic relationship between lesion length, MLA (by IVUS), and FFR remains under investigation. It is likely that longer, diffuse lesions with larger IVUS-derived MLA might be ultimately found to harbor greater physiological significance than short, focal lesions with lesser MLAs. The clinical implications of these relationships are also uncertain.

In the absence of corresponding physiological measurements, IVUS-based criteria of ULMCA lumen compromise per se have been successfully used to solely guide clinical decision making. Fassa et al. (39) identified the "normal" range of ULMCA MLA values as those that were confined to within 2 SD on either side of the mean of ULMCA MLA sampled from 121 consecutive patients with angiographically normal ULMCA lesions at their institution. Accordingly, the lower range of normal ULMCA MLA equated to 7.5 mm^2 in their population sampled (39). After this, 214 patients with angiographically ambiguous ULMCA lesions underwent IVUS. Of the patients with a ULMCA segment IVUS MLA ≥7.5 mm^2, 87% were treated medically, whereas 86% of patients with an MLA <7.5 mm^2 were revascularized. All patients were followed for a mean period of 3.3 years, and no statistical difference in outcomes was found between these 2 patient groups.

A recently published study evaluated the safety of a lower predefined IVUS MLA threshold of 6 mm^2 to guide decision making in a prospective multicenter study (40). An IVUS-derived ULMCA segment MLA of 6 mm^2 was previously shown to be a much closer IVUS (structural) correlate of an FFR of 0.75 across an angiographically indeterminate ULMCA lesion (24) and hence thought to be a more representative and appropriate threshold on IVUS. Accordingly, a total of 354 patients were enrolled in 22 centers. In 179 patients with a ULMCA segment MLA of ≥6 mm^2, revascularization was deferred (although permitted for non-ULMCA lesions), whereas the remaining 152 patients with an MLA <6 mm^2 were revascularized (45% with PCI and 55% with CABG). Importantly, the 2-year event-free survival of cardiac death and myocardial infarction (MI) was 97.7% in those patients who had no ULMCA revascularization, compared with 94.5% in the revascularized group (p = 0.5) (40). The results of this study provide further support for the utility of IVUS alone in guiding an appropriate treatment strategy for patients with angiographically indeterminate ULMCA stenoses. Although an MLA of 6 mm^2 was shown to be a valid cutoff for clinical decision making, yielding acceptable long-term clinical results, it is conceivable that lower MLA cutoff values might ultimately be shown to yield similarly acceptable long-term clinical outcomes (Table 2).

Table 2. Summary of Studies Using IVUS to Determine the Significance of ULMCA Disease

First Author (Ref. #)	N	FU (Months)	Outcome	IVUS Criterion for Significance	Comment
Abizaid et al. (36)	122	12	MACE	MLD	No specific cutoff suggested. LMCA MLD >3 mm portends incremental risk, also determined by comorbidities and coronary artery disease in other territories
Ricciardi et al. (37)	107	29	MACE	MLA	No specific cutoff suggested. MLA was a predictor of cardiac events
Legutko et al.*	44	44	Ischemia	MLD, MLA	MLA <8 mm^2 and MLD <2.8 mm correlated with FFR ≤ 0.75 and ischemia on 99Tc-Mibi-Spect
Jasti et al. (24)	51	11	Ischemia	MLD, MLA	MLA ≤ 5.9 mm^2 and MLD ≤ 2.8 mm. FFR of ≤ 0.75 used as gold-standard reference
Fassa et al. (39)	214	40	MACE	MLA	MLA <7.5 mm^2
de la Torre Hernandez et al. (40)	354	24	MACE	MLA	MLA <6 mm^2
Kang et al. (38)	55	NA	Functional	FFR	IVUS-derived MLA of <4.8 mm^2 correlated with FFR <0.80

*Legutko J, Dudek D, Rzeszutko L, Hubalewska A, Wizimirski M, Dubiel J. Invasive assessment of the borderline left main coronary artery stenosis—comparison with 99Tc-MIBI SPECT. Eur Heart J 2004;25:429(P2425).

IVUS = intravascular ultrasound; LMCA = left main coronary artery; MACE = major adverse cardiovascular events; MLA = minimum lumen area; MLD = minimum lumen diameter; other abbreviations as in Table 1.

True Distribution of LMCA Plaque: Insights From IVUS

Intravascular ultrasound has recently been used to highlight the complexity of distribution, burden, and composition of atherosclerotic plaque within the LMCA segment. A sound appreciation of these factors is crucial for planning and executing the optimal approach for PCI of the ULMCA lesion at hand. The length of the LMCA segment has been found to be an important factor in determining the predominant distribution of plaque, such that longer-length (>10 mm) LMCA segments have been shown to harbor significantly more plaque burden within the distal bifurcation region, compared with shorter (<10 mm) LMCA segments that harbor a slightly greater preponderance for plaque to distribute at the LMCA ostium (41). This study also revealed ostial LMCA lesions to have less overall plaque burden, greater degrees of negative (constrictive remodeling) and less calcification than nonostial LMCA lesions.

Percutaneous coronary intervention of bifurcation ULMCA lesions have traditionally posed a greater challenge for achieving MACE rates similar to those achieved with PCI of ostial ULMCA lesions (42). Although this might in part be a reflection of the stenting technique (43) and/or limitations of contemporary stent technologies (44), a lack of appreciation of the true extent, morphology, and true distribution of the LMCA bifurcation plaque within both daughter branches (LAD and LCX) is also a critical factor. Oviedo et al. (45) recently highlighted the inaccuracy of angiography alone for classifying LMCA bifurcation lesions. Contrary to findings upon angiography, IVUS identified the diffuse nature of atherosclerosis involving not only the parent (LMCA) segment but also both flow dividers (LAD and LCX). Although the carina was always spared, continuous plaque from the LMCA segment to the

proximal LAD was seen in 90% and in 62% of occasions to the proximal LCX segment (45). Bulky calcification might preclude appropriate lesion modification before stent implantation, which inevitably leads to stent underdeployment. On IVUS, the independent predictors of LMCA segment calcification were found to be related to prior CABG (protected LMCA segments), increasing age, Caucasian race (vs. Asian), and bifurcation location (46). Additionally, radio frequency analysis of IVUS data has shown that the ostial/proximal segment of the LAD contains greater amounts of complex (necrotic core and calcification) plaque than the LMCA segment itself; however, this requires further validation (46). Finally, in the setting of distal/bifurcation LMCA lesions, the importance of conducting dual IVUS pullbacks from within both the LAD and LCX branches has been highlighted (47). This is due to the relative inaccuracy of assessing lumen dimensions within the side branch ostium with IVUS (which significantly overestimates real lumen diameters) from the main vessel, compared with the direct assessment of each side branch respectively.

Intravascular ultrasound also plays a pivotal role in assessing plaque shift, especially after PCI of distal/bifurcation ULMCA lesions, and is also critical for the optimization of post-procedural MLA after PCI to reduce restenosis rates. It has been shown that, irrespective of the technique used for stenting bifurcation lesions with drug-eluting stents (DES), the commonest site of restenosis invariably occurs at the ostium of the side-branch (43), whereby the final post-intervention MLA at the ostium of the LCX branch was the only significant predictor of restenosis. For those patients who underwent a single crossover stent strategy, a post-intervention ostial LCX MLA of ≥ 4 mm^2 was associated with a restenosis rate of

6% compared with 50% in those whose ostial LCX MLA was ≤4 mm^2 (p = 0.04). Similarly in those who received 2 stents, a post-intervention ostial LCX MLA of ≥5.5 mm^2 was associated with a restenosis rate of 15% compared with 67% in those whose ostial LCX MLA was ≤5.5 mm^2 (p = 0.03). Although no published data currently exist for describing the optimal post-procedural MLA of the LMCA main-branch, expert consensus would recommend post-dilating the main branch to >8.5 mm^2 to reduce the rate of target lesion revascularization, while aiming for an MLA of >5.5 mm^2 for the ostia of each daughter branch (48).

Does the Use of IVUS-Guided PCI Within the ULMCA Segment Improve Clinical Outcomes?

Despite suggestive evidence to the contrary, there is still a general consensus within the interventional cardiology community that IVUS-guided stent implantation has a limited role in routine daily practice for demonstrating clinical benefit. As such, in North America, the general rate of IVUS use has struggled to climb beyond 10% of all PCIs performed (13). The use of IVUS to optimize lesion dilation was first proven to be clinically beneficial during the plain old balloon angioplasty era (49,50). After this, a number of trials demonstrated immediate procedural and clinical benefits of an IVUS-guided approach during PCI (51–56). However, the advent of DES with accompanying observations of remarkably low rates of in-stent restenosis perhaps contributed to the stifling of the emerging enthusiasm to undertake IVUS-guided PCI. Almost fittingly, however, IVUS proved crucial for understanding the mechanisms of stent thrombosis (and restenosis) that were observed after suboptimal DES deployment as well as using longer stents (57–59). Accordingly, IVUS guidance during DES implantation has been found to significantly reduce stent thrombosis rates and the need for repeat revascularization (11) as well as the short-term (30 days) and long-term (2 years) rate of death and MI, with similar evidence of benefit found during complex bifurcation stenting (60).

There is a dearth of appropriately designed studies examining whether similar benefit is derived during PCI of ULMCA segments. The lack of a systematic randomized trial has meant that the current level of evidence exists from retrospective analysis of registry data coupled with expert opinion. Initial comparisons between differing centers focusing on the effect of IVUS-guided ULMCA PCI yielded conflicting results. Agostoni et al. (61) showed no long-term clinical benefit of IVUS-guided ULMCA in 58 patients, whereas Park et al. (62) showed clear 1-year reductions in MACE in 102 patients. In a similar fashion, both centers have recently reported vastly differing rates of long-term clinical outcomes after ULMCA PCI (4-year all-cause mortality 35% in Onuma et al. [63] study vs. 6% in Park et al. [64] study). A closer analysis of these respective cohorts

reported from each center reveal important differences in patient and procedural characteristics that no doubt contributed to the vastly differing clinical outcomes. Onuma et al. (63) included patients that were older (65 vs. 61 years) and had worse left ventricular function (45% vs. 59%) and significantly higher operative risk (SYNTAX score of 39 vs. Euroscore of 3.3 in Park et al. [64]) and also included patients in cardiogenic shock (9% vs. 0%) or had an acute MI (23% vs. 0%), compared with the comparative results presented by Park et al. Importantly, Park et al. report a 90% rate of IVUS-guided ULMCA PCI compared with 30% in the cohort described by Onuma et al. Collectively, these results suggest an influence of patient comorbidities and procedural characteristics upon long-term outcomes after ULMCA PCI.

The most comprehensive data published to date on whether IVUS-guided ULMCA PCI yields superior clinical outcomes than angiography-guided ULMCA PCI stems from a post-hoc analysis from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty vs Surgical Revascularization) registry in which nonrandomized long-term clinical outcomes were evaluated in 975 patients (65). To account for the significant baseline differences between the 2 patient groups, propensity score matching was used to identify 201 "comparable" pairs of patients in each group. Kaplan-Meier incidence curves of log-rank 3-year outcomes revealed a significant lowering of the cumulative mortality rate within the IVUS-guided ULMCA PCI group receiving DES compared with the angiography-guided group (4.7% vs. 16%, p = 0.048). However, on multivariate analysis in all-comers (those receiving bare-metal stent and DES), there was a strong trend toward a statistically significant reduction in the rate of death at 3 years (hazard ratio: 0.54, 95% confidence interval: 0.28 to 1.03, p = 0.061).

Although these data suggest at the very least a marginal statistical clinical benefit of using IVUS-guided elective ULMCA PCI, there are some important limitations of this study worthy of mention. The inherent flaws of a nonrandomized study inevitably result in the real possibility of results being influenced by unmeasured confounders. Moreover, it seems that the study was not sufficiently powered to adequately compare the effectiveness of the 2 PCI strategies. Differences in acute procedural stent/vessel characteristics between the 2 groups were not reported. With an IVUS-guided PCI strategy, it would not be unreasonable to expect to see systematic reductions in target lesion revascularization; however, this was not observed. As such, the underlying mechanism for the observed reductions in mortality in this study remains elusive.

More recent data from Kang et al. (66) have shed some further light on the importance of evaluating the IVUS-derived MLA within the region of the distal LMCA

segment and origin of both daughter branches (termed "polygon of confluence," or POC) with IVUS before and after PCI. In the 168 patients with ULMCA segment bifurcation lesions undergoing PCI with 42 months of follow-up, the pre-PCI polygon of confluence MLA (a surrogate of the burden of distal LMCA disease) was an important predictor of the subsequent post-PCI minimal stent area that was achieved, which was also an important predictor of clinical events during follow-up. These data underscore the importance of performing optimal lesion preparation with IVUS-guidance before stent deployment for distal ULMCA lesions.

Summary and Author Recommendations

There is no other segment within the human coronary vasculature that is subject to such a significant degree of interobserver variability when assessing the degree of lumen compromise than the LMCA segment. Consequently, IVUS or FFR are strongly recommended when clinical suspicion arises as to the real significance of disease within the LMCA segment. It should be emphasized that the utility of these tools and the additional information gleaned from these invasive modalities should be carefully placed into the appropriate context with regard to patient clinical presentation. Fractional flow reserve provides a true in vivo determination of the physiological significance of LMCA lesions, without any information on structural extent and distribution of disease. Short of a large-scale randomized trial, there is emerging validation of its long-term safety and appropriateness for guiding decision making for angiographically indeterminate ULMCA stenoses. However, caution needs to be applied when using this technique in the setting of diffuse downstream as well as remote coronary arterial disease, because these will inevitably influence the FFR across the ULMCA segment per se. It is also important to emphasize that intravenous adenosine should be used for stimulating hyperemia, with an appropriate pull-back recording undertaken to allow localization of the disease within the LMCA segment or within daughter vessels. For evaluation of ostial LMCA lesions, care must be taken to disengage the guiding catheter during FFR measurements to prevent pressure dampening and an artificial increase in the FFR measurement obtained. Distal/bifurcation ULMCA stenoses require a dual FFR pullback. Furthermore, for FFR values within the gray-zone of 0.75 to 0.80, many experts would recommend the adjunctive use of IVUS in this setting. As such, FFR might be more suited for the evaluation of true ostial LMCA stenoses. If PCI is chosen as the likely mode of ULMCA revascularization, then we strongly recommend the use of IVUS, particularly for guiding the appropriate interventional strategy with immediate post-PCI evaluation of adequacy of stent deployment.

The strongest, most consistent LMCA segment parameter on IVUS that correlates with an FFR threshold of ≤ 0.75 and clinical outcomes is an IVUS-derived LMCA segment MLD threshold of ≤ 2.8 mm. An IVUS-derived MLA of 5.9 mm^2 also correlated with an FFR threshold of ≤ 0.75. Moreover, an IVUS-derived MLA of 6 mm^2 has been shown to an acceptable cutoff for guiding an LMCA lesion revascularization strategy. Therefore, on the basis of the published data to date, it seems reasonable to recommend an MLA of <6 mm^2 or an MLD of ≤ 2.8 mm as the designated IVUS-derived thresholds for specifically identifying prognostically significant LMCA segment disease and thus guiding treatment strategy. Although more recent reports would suggest an MLA of 6 mm^2 as being a conservative estimate of true functional significance of the ULMCA stenosis (38), such associations still warrant prospective clinical follow-up in a larger cohort of patients. We would also like to point out that, ultimately, patient comorbidities and the overall burden of atherosclerosis in other coronary territories strongly influence clinical outcomes, over and above a precise IVUS-derived threshold for ULMCA significance.

From a technical viewpoint, once the assessment and decision for PCI of the ULMCA segment lesion has been made, we recommend IVUS pullbacks to occur within both daughter branches when diffuse or distal LMCA disease is present. The smallest direct MLA/MLD of the distal ULMCA segment and ostia of each daughter branch should be noted. Careful attention should also be made to the degree of calcification present, and strong consideration should be given to plaque modification techniques if circumferential calcium is present. For distal/bifurcation ULMCA lesions, every effort should be made to achieve the greatest possible lumen dimensions before stent deployment, and iterative post-dilation should be performed to achieve a minimum stent area of >8.5 mm^2, origin LAD >5.5 mm^2, and origin LCX >5.5 mm^2 (48). It is also imperative for the guiding catheter to be positioned in a coaxial fashion to optimize the accuracy of IVUS parameters obtained. To better define the true position of the ostium for accurate stent positioning, the IVUS transducer can also be used in such a way to obtain the optimal angiographic view for stent deployment and appropriate marking of the exact positions of interest (Fig. 4: IVUS marking of the LMCA ostium with the "Sepal" wire technique) (67).

Conclusions

It is highly unlikely that there will ever be a randomized trial designed to test the efficacy of IVUS-guided PCI of ULMCA stenoses. The eagerly anticipated results of the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main
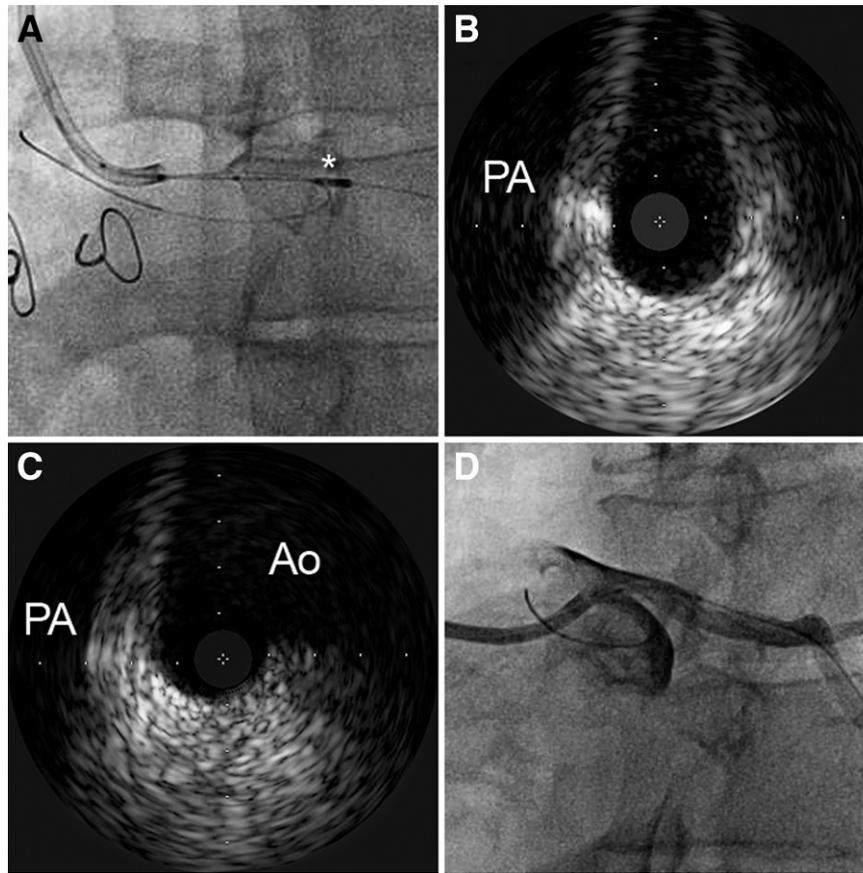
Figure 4. "Sepal" Wire Technique

The "Sepal" wire technique for aorto-ostial left main coronary artery (LMCA) stenting in a patient who presented with syncope and was found to have extrinsic LMCA compression by the pulmonary artery (PA). **(A)** An additional workhorse coronary guidewire seated within the aortic (Ao) cusp ("Sepal" wire), with intravascular ultrasound marking of the true ostium taking place **(white asterisk)**. **(B)** The slit-like compression of the LMCA from the PA; **(C)** the aorto-ostial region of the LMCA. The "Sepal" wire enables the guiding catheter to be withdrawn from the LMCA ostium, and Ao cusp injection allows identification of relevant anatomical landmarks. Additionally, fine positioning of the stent can be undertaken, because the anchor provided by the "Sepal" wire prevents the guiding catheter from being "sucked" into the LMCA when one pulls back with the stent to cover the ostium (**D** shows optimal positioning of the stent according to intravascular ultrasound marking).

Revascularization) trial will help further ascertain the utility of IVUS-guided PCI for ULMCA lesions. Existing trials point to the improvement of procedural and clinical outcomes when IVUS is used to optimize PCI within the epicardial coronary tree. For ULMCA PCI, however, the existing level of evidence for using IVUS-guided PCI is less robust. Nevertheless, the cumulative weight of existing data coupled with expert opinion would suggest that adjunctive imaging techniques (IVUS and/or FFR) be used liberally to assess the underlying significance of ambiguous ULMCA lesions on angiography. Furthermore, given the potential dire clinical consequences of procedural failure resulting in stent thrombosis or restenosis within the ULMCA segment, IVUS-guidance should be strongly recommended as the standard of care during ULMCA PCI.

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