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INTRAVASCULAR IMAGING (A. TRUESDELL, SECTION EDITOR)

Measure Twice, Cut Once: Adjunctive Physiology and Imaging in Left Main PCI

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Abstract

Purpose of Review While left main coronary artery (LMCA) disease is often evaluated based on angiographic findings, technical limitations of angiography or the presence of intermediate disease can make accurate lesion assessment difficult.

Recent Findings The rise of intravascular imaging and functional assessment of coronary artery disease lesions over the past 20 years has greatly improved PCI outcomes, making it an acceptal alternative to CABG in selected patients and lesions (Class IIa recommendation, after multidisciplinary Heart-Team discussion). We reviewed the advances of intravascular imaging (IVUS and OCT) and functional assessment (*FFR* and *iFR*) over the last 5–10 years specifically as it pertains to left main coronary artery disease. Functional assessment of the left main coronary artery and its bifurcations can help decide which lesion needs intervention.

Summary Intravascular imaging prior to and after PCI of lesions involving the left main and its bifurcations leads to decreased frequency of PCI complications, and more importantly, better long-term outcomes for the patient owing to a decreased frequency of target-vessel and target-lesion revascularization.

Keywords Left main · PCI · IVUS · *FFR* · Coronary artery disease · Intravascular imaging · Intermediate lesion assessment

Introduction

While left main coronary artery (LMCA) disease is often evaluated based on angiographic findings, technical limitations of angiography or the presence of intermediate disease can make accurate lesion assessment difficult. The presence of bifurcation lesions, ostial lesions, eccentric plaque formation, calcific nodules, overlapping coronary artery branches, and short LMCA can limit the ability of angiography to fully define disease in this territory [1••, 2]. Further assessment for lesion severity can focus on the anatomic features of the lesion or the hemodynamic impact of the lesion. Anatomy is examined using intravascular imaging modalities such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT). Functional or hemodynamic significance can be measured using fractional flow reserve (*FFR*). This paper will review the assessment of lesions involving the LMCA specifically to guide interventions and ensure optimal procedural results.

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Anatomic Assessment of Left Main Coronary Artery Lesions

IVUS studies of the LMCAdemonstrated that distal LMCA plaque is rarely focal, but rather much more commonly diffuse, involving the ostia of the left anterior descending (LAD) and/or left circumflex (LCx) artery as well [3]. The reverse is also true: disease in the ostial LAD or LCx is rarely focal and commonly involves the distal LMCA. The diffuse nature of the disease makes it difficult to assess the size of the non-diseased segment, leading to underestimation of disease severity. Consequently, angiographic interpretation of LMCA disease severity has the greatest inter-observer variability among the coronary arteries and is particularly poor in intermediate (50–70%) lesions [4].

Untreated LMCA disease has significant morbidity and mortality [5]. While coronary artery bypass grafting (CABG) is the gold standard for the treatment of complex LMCA disease, advances in PCI and medical therapy have led to an improvement in outcomes of percutaneous therapy. Multiple clinical trials and registry datasuggest that LMCA PCI may be as safe, effective, and comparable to CABG in terms of procedural success as well as long-term outcomes in selected patients and lesions (see Table 1) [12, 13].

IVUS and OCT imaging allow for direct intra-vascular interrogation of the arteries and can overcome some of the limitations of angiography's two dimensional "lumenograms." IVUS uses high-frequency sound waves (20–60 MHz range) emitted from a catheter tip to visualize the echogenic portions of the blood vessel wall lining, atheromatous disease in the wall and connective tissue covering the outer surface of the blood vessel. The blood and healthy muscle tissue are echo-lucent. Calcification in the vessel wall is very echogenic, which leads to shadowing behind the calcium as the majority of the sound wave is reflected back. OCT, on the other hand, emits near-infrared light waves from an intravascular catheter to penetrate surrounding tissues, producing real-time images of much higher resolution than IVUS. However, the limited ability of light waves to penetrate into tissue means that OCT imaging depth is lower than that of IVUS.

Technical Approach for LMCA Intravascular Imaging

When performing IVUS in the LMCA, it is important to disengage the guiding catheter from the left main ostium to allow complete visualization of the vessel. In addition, IVUS should be used to image both the LAD and LCx arteries on pullback into the LMCA, as 62% of patients with distal LMCA disease have plaque in both the LAD and LCx arteries as well [3]. The *MLA* measured when the IVUS catheter is pulled back from the LAD can be different from the *MLA* measured when the catheter is pulled back from the LCx due to the different angle each artery takes off the LMCA creating an oblique IVUS image leading to a falsely-larger cross-sectional area, so the smaller *MLA* should be used. On the other hand, OCT has significant difficulty imaging the ostium of the LMCA as it enters from the aorta because it is very difficult to completely clear the blood from that area while simultaneously disengaging the guide catheter. One novel solution to this problem is to perform OCT via light permeable guide-extension catheter [14].

Lesion Assessment and PCI Planning

IVUS and OCT can be used to confirm the presence and extent of LMCA disease after assessment by angiography, and can help show lesion characteristics and supplement physiologic assessment of lesion severity in an effort to guide pre-intervention planning. The Spanish Working Group on Interventional Cardiology (LITRO) found a significant increase in cardiac mortality and MI at 2 years in patients with a minimal luminal area (*MLA*) of less than 6.0 mm^2 as measured by IVUS compared to patients with an *MLA* of 6.0 mm^2 or greater, suggesting it is safe to defer intervention if the $MLA > 6.0\ mm^2$ [15]. A South Korean study comparing IVUS *MLA* with invasive physiologic assessment (*FFR*) in 55 patients with LMCA disease found that *MLA* of $< 4.8\ mm^2$ was the best predictor of an $FFR < 0.80$; however this study included many patients with non-isolated LMCA disease [16•]. In addition, this study was in a primarily Asian population that is known to have smaller disease-free coronary arteries than the Caucasian population [17]. Table 2 shows the four main IVUS studies that evaluated *MLA* compared to another benchmark measurement or survival data. It is therefore reasonable to suggest that a lesion is significant if it has an $MLA \leq 4.8\ mm^2$, defer intervention if $MLA \geq 6.0\ mm^2$, and to perform further testing (such as invasive functional assessment) if the *MLA* is between 4.8 and 6.0 mm^2 [20].

Once the decision is made to proceed with PCI of the LMCA (typically after multidisciplinary Heart Team discussion), IVUS should be used pre-intervention to help define the plaque characteristics and distribution of disease to aid in procedural planning. In a meta-analysis of 7 randomized controlled trials with a total of 3,192 patients, IVUS-guided second-generation DES implantation was found to have a lower risk of MACE, target-vessel revascularization (TVR), and target-lesion revascularization (TLR)

Table 1 Trials of PCI vs CABG in LMCA disease

Trial	Study time	Last update	Stent type, if specified	Median length of study	# sites	n	Syntax score (mean)	% DM	% ACS	% Multi-vessel disease	Primary endpoint (PCI vs CABG)	Other outcomes (PCI vs CABG)
EXCEL [6]	2010–2014	2019	Everolimus DES	5 years	126	1905	21	29	24	51	Composite death, stroke, MI: 22.0% vs 19.2% ($p=0.13$)	Death from any cause (13.0% vs 9.9%) CV death (5.0% vs 4.5%) MI (10.6% vs 9.1%) Cerebrovascular events (3.3% vs 5.2%) Ischemia-driven revascularization (16.9% vs 10.0%)
PRECOMBAT [7]	2004–2009	2020	Sirolimus DES	11.3 years	13	600	25	32	45	73	Composite death, MI, stroke, ischemia-driven revascularization: 29.8% vs 24.7%	Death, MI, stroke (18.2% vs 17.5%) All-cause mortality (14.5% vs 13.8%) Ischemia-driven TVR (16.1% vs 8.0%)
SYNTAX [8]	2005–2007	2019	TAXUS paclitaxel DES	10 years	85	1800	29	25	30	60	All-cause death: 28% vs 24%, $p=0.066$	LM disease death: 27% vs 28% Triple-vessel disease death: 28% vs 21%
MAIN-COMPARE [9]	2000–2006	2018	BMS 2000-May 2003 DES May 2003–2006, 77% sirolimus DES, 23% paclitaxel DES	12 years	12	2240	n/a	31	10	84	Composite death, MI, stroke: 25.0% vs 24.6%, HR 1.16, $p=0.19$	Death any cause: 22.2% vs 21.4%, HR 1.09, $p=0.48$ TVR: 22.6% vs 5.4%, HR 4.07, $p<0.001$
LE MANS [10]	2001–2004	2016	BMS 65% DES 35%	9.8 years		105	25	18	35	82	LVEF at 10 yrs 54.9 ± 8.3% vs 49.8 ± 10.3%, $p=0.07$	MACE (cardiovascular and cerebral) events 52.2% vs 62.5% Death any cause 21.6% vs 30.2% MI 8.7% vs 10.4% Repeat revasc 26.1% vs 31.3% None are statistically significant differences

Table 1 (continued)

Trial	Study time	Last update	Stent type, if specified	Median length of study	# sites	n	Syntax score (mean)	% DM	% ACS	% Multi-vessel disease	Primary endpoint (PCI vs CABG)	Other outcomes (PCI vs CABG)
NOBLE [11]	2008–2015	2020	BP-DES DP-DES	4.9 years	36	1201	22	15	17	Not reported	MACCE 28% vs 19%, $p=0.0002$	Death any cause 9% vs 9% Non-procedure MI 9% vs 3%, $p=0.0002$ Repeat revasc 17% vs 10%, $p=0.0009$

DM, diabetes mellitus; *ACS*, acute coronary syndrome; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *DES*, drug-eluting stent; *BMS*, bare-metal stent; *MI*, myocardial infarction; *CV* death, cardiovascular death; *TVR*, target-vessel revascularization; *MACE*, major adverse cardiovascular events; *LVEF*, left ventricular ejection fraction; *BP-DES*, biodegradable polymer drug-eluting stent; *DP-SES*, durable-polymer drug-eluting stent

than angiography-guided PCI [21]. IVUS can accurately define side-branch disease to determine if a provisional or an upfront two-stent strategy is best suited for management of the bifurcation. In addition, IVUS can accurately define the extent of coronary plaque calcification and presence of calcific nodules to help guide need for adjunctive therapies (such as orbital or rotational atherectomy or coronary lithotripsy) to help prevent stent under-expansion. Intra-vascular imaging allows the operator select optimal stent sizing by accurately measuring the vessel diameter and lesion length. IVUS-guided PCI has been shown to reduce long-term composite of cardiac death, MI, or TLR (5.6% IVUS-guided vs 10.7% angiography guided, $p=0.001$), and specifically reduce ischemia driven revascularization (4.8% of the IVUS-guided group vs 8.4% in the angiography-guided group ($p=0.007$) [22].

PCI Optimization

After stent implantation, IVUS imaging should be performed to help optimize stent implantation by assessing for the following: stent under-expansion, adequate lesion coverage, malapposition, or presence of edge dissection. Stent under-expansion is the single greatest predictor of stent failure, especially in-stent restenosis (ISR), stent thrombosis (ST), and TLR [23]. Kang et al. found a significant increase in ISR at 9 months after LMCA PCI if the post-stenting minimal stent area (MSA) was less than or equal to 5.0 mm^2 for the LCx ostium, 6.3 mm^2 for the LAD ostium, 7.2 mm^2 for the polygon of confluence (POC—area between LMCA and LAD-LCx bifurcation), and 8.2 mm^2 in the proximal LMCA above the POC, hence the "5–6-7–8 Rule" [24].

Stent malapposition is defined as a lack of contact of at least one stent strut with the underlying intimal wall of the artery in a segment not overlying a side branch. It most commonly occurs in presence of severe lesion calcification or ectasia or with stent under-expansion. Because at least one stent strut is not in contact with the intimal wall, the concern is that this will lead to decreased drug delivery to the intimal wall and heterogenous neo-vascularization leading to increased risk of stent thrombosis. Figure 1 shows a case of stent under-expansion and malapposition, and Fig. 2 demonstrates the importance of imaging after PCI. Except for proximal stent edge malapposition, acute stent malapposition in LMCA PCI is not associated with an increased risk of cardiac events [24]. Stent deformation can be diagnosed with IVUS, and typically occurs if the proximal edge of the stent is pushed forward by a guide catheter. If identified, stent deformation should be corrected by additional ballooning or placement of another stent to avoid high rates of LMCA-related MI (19.9% ischemia-driven TLR in patients with stent deformation, compared to 8% without) [25].

Table 2 IVUS parameters in various studies and registries

Study	Type	Inclusion criteria	Study time	Population/ethnicity	Comparator	*MLA* IVUS
Jasti et al. [18]	Observational	Angiographically ambiguous LMCA	2000–2003	$n=55$ Louisville, KY	*FFR* < 0.75 or *FFR* ≥ 0.75	*MLA* ≤ 2.8 mm^2 strongly predicts *FFR* < 0.75 *MLA* ≥ 5.9 mm^2 strongly predicts *FFR* < 0.75
LITRO study [15]	Prospective validation trial	Angiographically intermediate unprotected LMCA If *MLA* by IVUS ≤ 6 mm^2, proceed with revascularization	2007	$n=354$ 22 centers in Spain	2-year follow up, MACE, death, event-free survival in both groups	Cardiac death-free 97.7% in deferred group and 94.5% in revascularization group Event-free survival 87.3% vs 80.6%
Kang et al. [16]	Observational	Patient with angina and 30–80% LM lesion	2010–2011	$n=55$ South Korea	*FFR* < 0.80 and *FFR* < 0.75	*MLA* < 4.8 mm^2 predicts *FFR* < 0.80 (89% sensitivity, 83% specificity) *MLA* < 4.1 mm^2 predicts *FFR* < 0.75 (95% sensitivity, 83% specificity) *MLA* ≥ 4.1 mm^2 predicts *FFR* ≥ 0.75 (79% sensitivity, 80% specificity)
Park et al. [19]	Observational	Isolated ostial or shaft intermediate (30–80%) LMCA stenosis	2010–2012	$n=112$ South Korea	*FFR* ≤ 0.80	*MLA* ≤ 4.5 mm^2 predicts *FFR* ≤ 0.80

MLA, minimal lumen area; *IVUS*, intravascular ultrasound; *LMCA*, left main coronary artery; *FFR*, fractional flow reserve; *MACE*, major adverse cardiovascular events; *LM*, left main

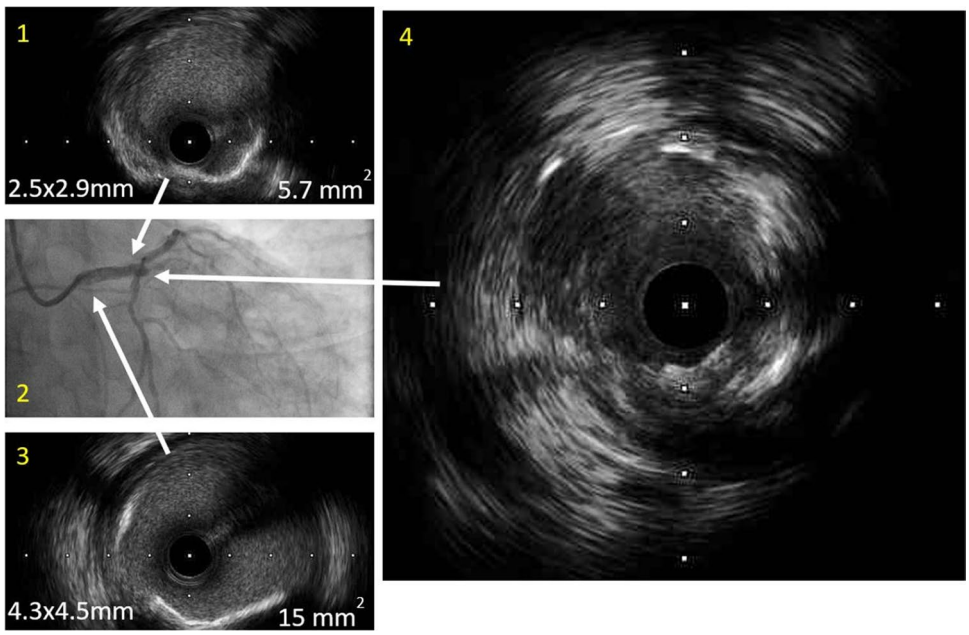

Fig. 1 Stent under-expansion resulting in stent thrombosis 8 months after PCI to LAD. A seventy-five year-old male was diagnosed with 3-vessel CAD 8 months ago but declined for CABG so underwent PCI to LAD and ostial Ramus. He was compliant with dual antiplatelet therapy but presented 8 months later with dyspnea, found to have newly reduced LV ejection fraction of 30%. He underwent LHC which showed stent under-expansion, malapposition, and stent thrombosis. Panel 2 shows coronary angiogram, with arrows pointing to IVUS images. Panel 3 shows IVUS of proximal LM to be sized 4.3 × 4.5 mm, 15 mm^2 area. Panel 1 shows IVUS of distal LM to be sized 2.5 × 2.9 mm, 5.7 mm^2 area. Panel 4 shows IVUS of Ramus stent, showing stent under-expansion and stent thrombus

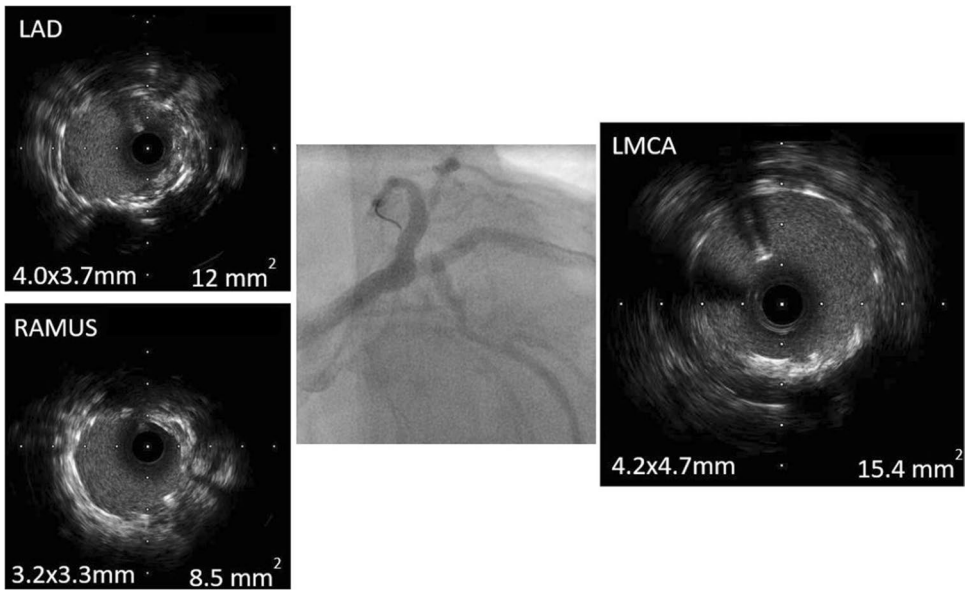

Fig. 2 IVUS imaging after PCI to LAD and ostial Ramus extending back to LMCA confirm well-expanded stents exceeding minimal stent area recommendations

Clinical Outcomes of Intravascular Imaging in LMCA PCI

Several observational studies and meta-analyses of observational studies, as well as two small randomized controlled trials, demonstrated benefits of intravascular imaging over conventional angiography for LMCA PCI. A meta-analysis of 4 registries of patients undergoing DES PCI for unprotected LMCA disease showed significantly lower MACE, TLR, and stent thrombosis at 3 years in the IVUS-guided group compared to the conventional angiography group [26]. A recent randomized controlled trial of 336 consecutive patients who were undergoing PCI for unprotected LMCA disease between December 2010 to 2015 found a significantly reduced risk of MACE at 1 year (13.2% vs 21.9%, $p=0.031$) in the IVUS-guided group compared to the angiography-guided group with most of the improvement in MACE being driven by a reduction in the risk of cardiac death [27].

Comparative Efficacy of OCT and IVUS

Although there were many studies that compared IVUS or OCT to conventional angiography, only a few studies compared IVUS and OCT to each other. Because OCT has technical limitations in imaging the ostial LMCA, most of these trials excluded patients with LMCA disease. Table 3 summarizes the four major trials to-date that compared IVUS and OCT.

The first study to report on OCT-guided PCI for LMCA disease was the LEMON study in 2020 [32]. It was a pilot study of 70 patients with mid- or distal LMCA disease. The primary endpoint of TIMI 3 flow in all branches and adequate OCT stent expansion was achieved in 86% of patients, with 1-year event-free rate of 98.6%. There have not yet been any OCT vs IVUS-guided PCI studies in patients with LMCA disease.

Limitations of Intravascular Imaging for LMCA PCI

Despite all the above advantages of intracoronary imaging to help guide diagnosis and treatment of LMCA disease, there are several main disadvantages that should be discussed. Both IVUS and OCT are additional steps that take additional time, equipment, and expertise above what is needed for coronary angiography. Although IVUS is fully reimbursed as an additional procedure in Japan, it is not reimbursed separately in the USA but rather is bundled with the diagnostic angiography procedure. The extra equipment and time spent in the cardiac catheterization laboratory are not reimbursed extra in the USA, possibly leading to fewer operators using these imaging techniques on a routine basis. In 2011, it was estimated that only 15% of PCI procedures in the USA were guided by IVUS, while 70% of PCI procedures in Japan (mostly elective) used IVUS [33]. Because intravascular imaging involves additional steps, there are concerns they may lead to more complications. In a single center registry of 13,418 undergoing coronary angiography between April 2008 and December 2013, intra-vascular imaging-related complications were rare (OCT 0.6%, IVUS 0.5%), all were easily treatable within the catheterization lab, and none led to emergent surgery or patient death [34•]. OCT uses additional contrast, making it less appealing for patients with

Table 3 Studies comparing OCT and IVUS

Study	Year	Study type	Population	Outcomes (OCT vs IVUS)
ILUMIEN II [28]	2015	Matched-pair analysis (OCT used in this study, IVUS participants from ADAPT-DES study)	OCT $n=354$ IVUS $n=572$	Degree of stent expansion 72.8% vs 70.6%, $p=0.29$ Higher rate of post-PCI stent malapposition, tissue protrusion, edge dissection detected by OCT but no difference in major malapposition, tissue protrusion, dissection
ILUMIEN III [29]	2016	Randomized controlled trial OCT vs IVUS vs angiographically-guided PCI	$n=450$ 29 sites, 8 countries *excluded LMCA disease	Primary outcome minimal stent area after PCI: 5.79 mm^2 with OCT, 5.89 mm^2 with IVUS, 5.49 mm^2 with angiography
OPINION [30]	2017	Randomized controlled noninferiority trial of optical frequency domain imaging vs IVUS-guided PCI	$n=829$ *excluded LMCA disease	Primary endpoint: target vessel failure (cardiac death, target-vessel MI, ischemia-driven TVR) at 12 months Target vessel failure: 4.9% vs 5.2%, p-noninferiority 0.04 Secondary outcome: angiographic restenosis at 8 months In-stent restenosis: 1.6% vs 1.6%, $p=1.0$ In-segment restenosis: 6.0% vs 6.2%, $p=1.0$
MISTIC-1 [31]	2020	Randomized controlled noninferiority trial of optical frequency domain imaging (OFDI) vs IVUS-guided PCI	$n=109$ *excluded LMCA disease	Post-procedure *MLA* 6.31 mm^2 vs 6.72 mm^2, $p=0.29$ Primary outcome: in-segment *MLA* assessed by OFDI at 8 months, 4.56 mm^2 vs 4.13 mm^2, p-noninferiority <0.001 Secondary outcome: MACE, target-vessel MI, TLR at 3 years, 7.4% vs 7.3%, $p=0.95$

OCT, optical coherence tomography; *IVUS*, intravascular ultrasound; *PCI*, percutaneous coronary intervention; *LMCA*, left main coronary artery

pre-existing moderate or advanced renal disease not yet on dialysis; however, saline-mediated OCT imaging has been reported [35]. The advantages of intravascular imaging-guided PCI in terms of significantly better outcomes greatly outweigh the cost and time disadvantages, especially in higher-volume centers where these extra procedures can be built into the workflow, significantly decreasing cost and time of these extra steps [36].

Summary: Intravascular Imaging for LMCA PCI

Intravascular imaging with IVUS or OCT is a valuable tool that can help more accurately define LMCA disease severity, characteristics and help optimize PCI. Imaging-guided PCI has been shown to reduce the risk of stent malapposition and stent under-expansion, ensure adequate lesion coverage and diagnose stent edge dissection. Several studies have demonstrated benefits of IVUS over conventional angiography in LMCA disease, and several studies have demonstrated relatively comparable efficacy of OCT and IVUS in patients without LMCA disease, with future studies ongoing comparing OCT and IVUS in patients with LMCA disease. The efficacy and safety of image-guided PCI have led to IVUS being a core part of PCI practice recommendations, starting with ACC/AHA/SCAI practice guidelines in 2006 and followed by the ESC/EACTS guidelines in 2014 [37, 38]. Although these procedures are additional steps that take additional time and more specialized equipment, they are still not reimbursed as additional procedures so they are not used as frequently in the USA compared to Japan where they are fully reimbursed. This may be an appropriate future advocacy effort for Interventional Cardiologists in the USA.

Functional Assessment of Left Main Coronary Artery Lesions

The assessment of LMCA stenosis severity can be accomplished with intravascular imaging techniques as reviewed previously, or physiologically with pressure wire assessment either by fractional flow reserve (*FFR*) or instantaneous free-wave ratio (*iFR*). Assessment of severity based solely on intravascular imaging has limitations when it comes to functional assessment of LMCA stenosis, as there exists variability between patient populations. For example, as mentioned previously and shown in Table 2, the average normal left main minimal luminal area (*MLA*) on IVUS was 4.8 mm^2 in a Korean study, compared to an average of 7.6 mm^2 in an American study. Expectantly, the *MLA* cutoff for physiologically significant LMCA lesions by $FFR<0.80$ in the Korean

study was 4.5 mm^2 and the *MLA* cutoff for *FFR* < 0.80 in the American study was 5.9mm^2 [39]. Another study comparing LM lesions between Caucasian North American and Asian patients showed that Asian patients had a significantly smaller LMCA *MLA* (5.2 ± 1.8 mm2 versus 6.2 ± 1.4 mm2, respectively; $p < 0.0001$) [40]. LMCA imaging was reviewed in detail in the previous section.

Fractional Flow Reserve

Fractional flow reserve is a ratio between maximum flow in a diseased coronary vessel to maximum flow in a normal coronary vessel. A pressure wire is used to calculate the ratio between coronary pressure distal to the lesion and mean arterial pressure (aortic pressure) after induction of maximal hyperemia with adenosine. The cutoff value for abnormal fractional flow reserve (*FFR*) is ≤ 0.75, and this is associated with reversible myocardial ischemia that improved after revascularization [41]. More specifically to this discussion, multiple studies have demonstrated safety of deferring revascularization with an *FFR* cutoff ≥ 0.80 in the case of LMCA stenosis [42•, 43••, 44]. Due to its unique anatomy when compared with other coronary arteries, however, assessment of intermediate LMCA stenosis may be limited in the presence of downstream coronary stenosis which can lead to both underestimation or overestimation of lesion severity. *FFR* performance is particularly limited in evaluating LMCA stenosis when there is severe disease in both the LAD and LCx arteries. According to Fearon et al., in cases of LMCA stenosis with only one diseased side branch (LAD or LCx), the distal wire can be placed in the non-diseased side branch for more accurate measurement of LMCA flow [45]. If the *FFR* is > 0.80, the LMCA lesion is hemodynamically insignificant and if the *FFR* is ≤ 0.80, the LMCA stenosis can be considered hemodynamically significant. Fearon et al. note that with *FFR* between 0.81 and 0.85, hemodynamic significance remains indeterminate when the combined *FFR* of the LMCA and downstream disease is ≤ 0.45. In this situation, IVUS guidance is preferred as adjunct to determine need for revascularization with a recommended threshold minimal luminal area of < 6.0 mm^2 [46].

Resting Flow Reserve Indices: *iFR*, *DFR*, *RFR*

iFR is a tool for functional assessment of coronary lesion severity, but it does not require induction of hyperemia. *iFR* uses a specialized pressure wire to measure the ratio of distal coronary artery pressure to the pressure within the aorta, during a period of diastole known as the "wave-free period." Both diastolic hyperemia-free ratio (*DFR*) and resting full-cycle ratio (*RFR*) may be considered synonymous with *iFR*. The only difference comes down to separate manufacturers with proprietary measurement algorithms. The cutoff value for abnormal *iFR* associated with myocardial ischemia is ≤ 0.89. The DEFINE-FLAIR and iFR-SWEDEHEART trials demonstrated that deferral of revascularization was safe with *iFR* > 0.89. An *iFR* > 0.93 is considered non-ischemic but occasionally *iFR* falls in gray-zone between 0.86 and 0.93 at which time *FFR* can be considered [47, 48]. Similar to *FFR*, *iFR* also has limitations when it comes to evaluating LMCA stenosis even though the cutoff value for myocardial ischemia remains the same at ≤ 0.89. For non-LMCA lesions, *iFR* has been demonstrated to be non-inferior to *FFR*. Recent studies have demonstrated that *iFR* assessment of LMCA stenosis is as reliable as *FFR* but despite this, more studies are needed to confirm the role of *iFR* when managing intermediate LMCA stenosis [49, 50]. The ongoing iLITRO study (Concordance Between *FFR* and *iFR* for the Assessment of Intermediate Lesions in the Left Main Coronary Artery: A Prospective Validation of a Default Value for *iFR*) may further shed light on the use of *iFR* for the evaluation of intermediate LMCA stenosis.

Common Pitfalls of *iFR* or *FFR*

Evaluation of lesions by *iFR* or *FFR* can vary based on operator experience and technique. Proper technique of measuring fractional flow is essential, especially for LMCA disease. It is important to first set the pressure transducer at the level of the heart for accurate measurement of the aortic pressures. The pressure wire should be flushed and zeroed before being introduced into the body. Equalization of the pressure wire in the aorta should occur before the pressure wire is advanced into the coronary artery. Intracoronary nitroglycerin should be administered to reduce the vasomotor response to the wire in the coronary. The guide should be flushed with saline once the wire is advanced across the lesion. A resting gradient can then be obtained if performing *iFR*. If performing *FFR*, maximal hyperemia should be induced by administration of a hyperemic agent such as adenosine (either intravenously or intracoronary). Insufficient hyperemia when measuring *FFR* can lead to underestimation of gradients, overestimation of *FFR*, and underestimation of stenosis severity. Hyperemia is dependent on microcirculation, and this may be affected by a wide variety of conditions such as left ventricular hypertrophy, hypertrophic cardiomyopathy, aortic stenosis, amyloidosis, or diabetes mellitus.

When trying to determine the flow of an ostial LMCA lesion by *iFR* or *FFR*, it is necessary to disengage the guiding catheter at the time of functional assessment. As noted earlier, it is important with both *iFR* and *FFR* to perform equalization of the pressure wire in standard fashion while

in the aorta, before the measurement across the lesion is obtained. Equalization within the coronary, or with a guiding catheter deeply engaged in the coronary, may skew measurements leading to erroneous *FFR* or *iFR* results.

Conclusion: Functional Assessment of LMCA Lesions

Assessment of LMCA stenosis severity is limited when intravascular imaging or coronary angiography is used without flow-pressure functional assessment as there is great variability of LMCA size in different populations. Functional assessment with *FFR* or *iFR* adds great utility to the diagnosis and management of LMCA disease, and allows for more evidence-based decision-making when it comes to deciding on whether to intervene on a lesion.

Conclusion

Functional assessment of LMCA lesions and intravascular imaging of lesion characteristics are two complementary modalities that can be used to better assess a lesion's physiologic significance and anatomic characteristics. These modalities can be an invaluable addition to conventional coronary angiography before and after PCI, and several studies have shown improvement in patient outcomes, reduced risk of TLR and stent thrombosis, especially with LMCA PCI. Although they are more time-consuming to perform in the cardiac catheterization laboratory and are not reimbursed as additional procedures in the USA, their use is becoming part of routine practice for PCI operators in order to obtain the best outcomes for their patients.

Declarations

Competing Interests Shroff: Consultant-Terumo, CSI, Cordis, Abbott, Medtronic. All other authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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