The invasive intracoronary imaging assessment of left main coronary artery disease

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Abstract

Left main coronary artery disease is associated with an unfavorable prognosis. Evidence-based decision making regarding the optimal revascularization strategy in patients with left main disease has become a challenge, in view of the recently published data. An improvement in outcomes following left main percutaneous interventions could be achieved by reducing the rate of repeat target lesion revascularization through stent optimization techniques. In the setting of left main disease, procedural guidance by intravascular ultrasound or optical coherence tomography is essential for good long-term results, in such a way that intravascular imaging has gained more of a therapeutic connotation. Besides stent optimization, intracoronary imaging quantifies lesion severity, guides lesion preparation through morphological data, facilitates stent selection through accurate vessel sizing, identifies the landing zones, diagnoses acute vessel wall complications such as stent-related edge dissection or intramural hematoma, and defines procedural success.

This review focuses on the two main intracoronary imaging techniques used for diagnostic evaluation and procedural guidance in left main coronary artery disease: intravascular ultrasound and optical coherence tomography. Based on the most recently published data, the review discusses each technique’s advantages and pitfalls, and summarizes their indications.

Keywords: left main coronary artery disease; intracoronary imaging; intravascular ultrasound; optical coherence tomography; percutaneous coronary intervention

Introduction

Left main coronary artery (LMCA) disease is associated with an unfavorable prognosis, with three-year mortality rates as high as 63% in patients on medical therapy [1]. In the coronary revascularization era, the five-year mortality rates in patients with LMCA disease still exceed 10%, both after coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) [2], despite a relative risk reduction of almost 80% as compared to medical therapy alone [3]. The poor patient prognosis is mainly due to the anatomical importance of the LMCA and to the large amount of myocardium at ischemic risk supplied by its branches. As stated by the current practice guidelines, the key to improved patient outcomes in LMCA disease is the Heart Team discussion [4]. However, the process of evidence-based decision making regarding the optimal revascularization strategy in patients with LMCA disease has become a challenge, in view of the recently published data.

Revascularization strategies – current issues and uncertainties

The latest clinical practice guidelines from the American College of Cardiology/American Heart Association emphasize the location of the LMCA lesion in the selection of the most appropriate revascularization strategy [5]. In the case of isolated ostial or shaft LMCA lesions, PCI received a class IIa recommendation, whereas in the setting of distal LMCA bifurcation lesions or of those associated with complex multivessel disease, a class IIb was granted [5]. It must be mentioned, however, that a class I recommendation was conferred to CABG, as the treat-
ment of choice, whenever the clinical context favored it. Other key elements that must be considered include the anatomic complexity and the extent of coronary artery disease, the presence of diabetes mellitus, left ventricular systolic dysfunction, the acuity of clinical presentation, or the possibility of achieving complete revascularization in the setting of chronic total occlusions.

When comparing PCI with CABG, confusing and apparently discordant results have been recently presented, probably due to the different research methodologies and to the inclusion of heterogeneous groups of patients [2]. The results of The Evaluation of the XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial were published in 2019, an analysis of mortality at five years showing an excess risk in the PCI group (odds ratio 1.38, 95% CI 1.03–1.85) [6]. On the contrary, in The Nordic–Baltic–British Left Main Revascularization (NOBLE) trial, although the composite outcome of death, non-periprocedural myocardial infarction, stroke, and repeat revascularization was more frequent in the PCI group, no significant difference in mortality rates were observed between treatment arms (HR 1.08, 95% CI 0.74–1.59) [7]. A recent meta-analysis brought important new evidence to the issue, as it evaluated all the five randomized trials that compared PCI and CAGB in the setting of LMCA disease [8]. At a mean follow-up of 67 months, there was no difference in mortality between the two revascularization strategies. However, a higher rate of repeat revascularization and non-periprocedural myocardial infarction was observed in the PCI arm [8].

Considering the recently published data, an improvement in outcomes following left main PCI could be achieved by reducing the rate of repeat target lesion/vessel revascularization through stent optimization techniques. The issue is particularly relevant when contemplating the necessity for two stents implantation in LMCA bifurcation lesions. In this context, the judicious use of intracoronary imaging could reduce the gap between PCI and CAGB in the treatment of LMCA disease.

### Intracoronary imaging in LMCA disease

In LMCA disease, procedural guidance by intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is essential for good long-term results, in such a way that intravascular imaging has gained more of a therapeutic connotation [9]. Besides stent optimization, intracoronary imaging quantifies lesion severity, guides lesion preparation through morphological data, facilitates stent selection through accurate vessel sizing, identifies the landing zones, diagnoses acute vessel wall complications such as stent-related edge dissection or intramural hematoma, and defines procedural success.

Several studies have demonstrated improved outcomes in IVUS-guided LMCA disease PCI [10-13]. The clinical superiority of IVUS-guided procedures was in fact demonstrated irrespective of the affected coronary artery in an all-comer population [14]. In support of these data, a large recent meta-analysis demonstrated a significantly lower risk of all-cause death, cardiac death and stent thrombosis for IVUS-guided LMCA interventions [15]. A specific IVUS examination protocol was prospectively identified for LMCA assessment [13]. According to de la Torre Hernandez et al., a baseline assessment of the LMCA should be performed even in the presence of significant lesions, while in the setting of distal LMCA disease, the two main branches should be separately explored for the evaluation of ostial involvement [13]. The authors finally emphasized the importance of catheter co-axiality and guiding catheter disengagement from the main vessel during pullback, in case of ostial lesions [13]. Although the majority of LMCA lesions involve the bifurcation, there are only a few randomized trials specifically addressing stent optimization at this level [10,16,17]. Based on current evidence, the 2018 ESC/EACTS Guidelines on Myocardial Revascularization state that IVUS should be considered to optimize treatment of unprotected LMCA lesions (class IIa indication, level of evidence B) [4].

Concerning OCT, its much shorter wavelength compared to ultrasounds, enables it to provide higher resolution (10–20 μm) images than IVUS (150–200 μm) [18]. Conversely, tissue penetration of OCT is lower than with IVUS. The transmission of the light from the catheter to the vessel wall and back needs a blood free environment. Older systems obtained this by occluding the vessel with a balloon and flushing the lumen with saline solution. The new OCT devices can process data much faster. With a pullback speed of 10–40 mm/s, image acquisition usually takes 5–10 s. Accelerated pullback speeds permit the use of a single bolus injection of contrast to produce a blood-free environment, thereby eliminating the need for balloon occlusion [19].

The higher resolution of OCT over IVUS leads both to a more detailed preprocedural vessel imaging by identifying thrombus, lipid, calcium, fibrous cap thickness, or dissections and to a complete assessment of procedural success by characterizing struts apposition and stent expansion, and by diagnosing stent-related edge dissections, or tissue protrusion and thrombus. Instead, technical limitations of OCT become more obvious when imaging the left main. The lower field depth is particularly important in large vessels, such as the LMCA, where the
vessel diameter can regularly exceed 4 mm. Achieving a blood-free field might be difficult due to the high coronary flow [20]. In addition, as a well-engaged guiding catheter is needed to adequately displace the blood by iodine contrast injection, it inevitably obscures visualization of the LMCA ostium.

Notwithstanding the afore mentioned limitations, a recent study showed that LMCA was adequately assessed by OCT in more than 90% of the quadrants, most artefacts being located in the proximal segment [21]. The most commonly diseased LMCA segment is the bifurcation, where OCT imaging is accurate.

1. Lesion assessment
Coronary angiography is considered the gold standard for the diagnosis of coronary artery disease, but it has some inherent limitations. Angiographic evaluation of stenosis severity is based on the comparison to an adjacent reference segment. However, these segments could be diffusely diseased, either stenotic, or enlarged because of the Glagov remodeling phenomenon [22]. The lack of a normal reference segment may lead to the underestimation of lesion severity by angiography, major discrepancies being reported between the angiographic severity of stenoses and postmortem histologic evaluation [23,24]. In addition, several studies have demonstrated a significant inter-observer variability in the quantification of coronary artery stenoses by coronary angiography [24].

Quantitative coronary angiography (QCA) provides a more accurate quantification of lesion severity as compared to visual assessment, but its results are influenced by the same limitations as above.

LMCA has some anatomic and structural characteristics which make its lesions different from those affecting its branches and which mandate additional imaging evaluation: propensity for calcifications, a high elastic component that may hinder stent expansion and an increased frequency of distal tapering. On the other hand, LMCA has lower plaque burden and fewer thin-cap fibroatheromas (TCFA) than proximal left anterior descending (LAD) coronary artery.

1.1. Vessel sizing and bifurcation geometry
Both IVUS and OCT measure vessel size and plaque burden within the LMCA and its main branches realizing a more complex anatomic and structural evaluation than coronary angiography.

An IVUS determined minimal luminal area (MLA) of less than 6.0 mm² has been demonstrated as the optimal cutoff value for LMCA revascularization, with a sensitivity of 93% [25], and has subsequently been validated in a large clinical outcome study [13]. The 6.0 mm² cutoff value agrees with the theoretical value derived from fractal geometry. Using the currently established 3.0 mm² as the best MLA cutoff for the left main branches, the calculated left main MLA cutoff by linear law is 5.8 mm² [26,27]. It must be underlined that MLA cutoffs as low as 4.5 mm² have been derived from studies conducted in Asian populations. Their 75% negative predictive value is considered suboptimal in Caucasian patients, as one in four patients with severe ischemia would be missed [28]. Measurements of MLA by OCT are 10% lower than those performed by IVUS [29]. For example, in the large randomized Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION) trial, the chosen stent size was significantly smaller in the OCT arm as compared with the IVUS arm [30]. A possible explanation for the smaller MLA might be the greater resolution of OCT, which enables a sharper delineation of luminal borders and less tracing interpolation. Likewise, since OCT uses the visible lumen as a reference, rather than the external elastic lamina area, it might lead to smaller stent size selection and lower inflation pressures for stent optimization than with IVUS guidance [30].

An OCT-guided PCI strategy by performing MLA measurement at the level of the external elastic lamina was tested in the ILLUMIEN III study [18]. The strategy was safe and resulted in similar minimum stent areas as with IVUS-guided PCI [18]. However, MLA measurement based on the external elastic lamina has some drawbacks in large vessels with bulky plaques with necrotic cores, where lipids or macrophages present in the superficial layers of the plaque may hinder OCT imaging of the deeper components [19]. Nevertheless, with second-generation drug-eluting stents (DES) and large vessels like LMCA, the clinical impact of a small difference in stent diameter between OCT and IVUS-guided PCI most probably is not significant [18].

Due to the variations in the accepted IVUS-derived MLA thresholds in different populations, the OCT-derived MLA cutoff values are poorly established. Dato et al. have proposed the following revascularization strategy for LMCA disease: an OCT-measured stenosis of more than 75% should be treated regardless of the MLA value, while a stenosis between 50% and 75% should be stented in case of a rather conservative OCT-derived MLA cutoff of less than 4 mm² [31].

Dato et al. noticed that a remarkable proportion of patients with angiographically intermediate distal LMCA lesions are found to have severe lesions at the ostium of LMCA major branches [31]. Due to foreshortenings and overlapping in bifurcation lesions, angiography is limited for their quantitative evaluation. Both IVUS and OCT have obvious advantages in the assessment of ostial LAD and left circumflex lesions. Regarding the probability of...
side branch narrowing after a provisional stenting strategy, a spiky (“eyebrow” sign) carina appearance on IVUS and a narrower carina angle by OCT have been shown to predict carina shift towards the side branch lumen [32].

In addition, in planning distal LMCA stenting, OCT has the advantage of accurately assessing the bifurcation angle during pullback from the main branch, in longitudinal view. OCT scan range inside the bifurcation should be adjusted according to the proximal, larger vessel. Side branch ostium might be hindered by the guidewire shadow, therefore multiple pullbacks should be performed [19]. With 3D OCT it is easier to recognize the complex anatomy of the bifurcation and the effects of stenting. For example, the carina shift after stent deployment in the main branch is clearly viewed in the endoscopic 3D OCT mode. The newly developed 3D OCT software with a bifurcation mode automatically recognizes the carina and enables a quantitative assessment of the side branch ostium and plaque severity [19]. 3D OCT may also offer guidance in side-branch rewiring through the distal stent cell after main branch stenting [19]. Its use is also recommended to exclude accidental abluminal rewiring and to assess the position of the recrossing wire [19]. Considering the physiological significance of overhanging struts in front of the left circumflex or LAD ostium, the importance of 3D OCT should be even more emphasized [19]. Because of its high resolution, OCT may identify rare complications during complex bifurcation stenting techniques that would probably result in stent thrombosis, if left untreated, as our group previously reported [33].

1.2. Plaque composition

The evaluation of plaque morphology is essential for guiding lesion preparation. During OCT examination, plaque rupture, fibrous cap erosion, plaque-associated thrombus, and TCFA morphology are more frequently detected as compared to IVUS. OCT can identify these vulnerable plaques, by visualizing both their thin fibrous cap of less than 65μm and their necrotic core. Clusters of large macrophages with high lipid content may be identified by OCT as bright spots along the fibrous cap. Thrombus is also better imaged by OCT than IVUS, as even the discrimination between red and white thrombus is possible. Other features of instability, such as vasa vasorum inside lipid plaques or spontaneous dissections can be spotted and characterized by OCT [34,35].

Calcium nodules are clearly seen in OCT, with well-defined boundaries since light penetrates calcium, unlike sound in IVUS. Assessment of calcification by OCT could indicate what kind of lesion preparation should be performed (e.g. rotablation in case of superficial circumferential calcium deposits, or cutting balloon angioplasty in case of deeply situated calcifications), as the extension of calcifications at OCT is associated with stent underexpansion [19].

2. Procedural guidance and result assessment

Because of the extensive myocardial territory supplied by the left coronary artery, failure of left main stenting may have catastrophic clinical consequences both on the short and on the long-term, either due to stent thrombosis or to intrastent restenosis. Optimization of the immediate result in LMCA PCI is accomplished by intravascular imaging.

2.1. Stent underexpansion

The use of IVUS to guide stent implantation in LMCA lesions determined a significant clinical advantage according to recently published studies or registries [9,36,37]. Stent underexpansion is a major predictor of stent failure. However, there are no clear criteria regarding the targeted minimum stent area (MSA). Due to anthropomorphic and ethnic differences in LMCA size, the MSA should be reported to the distal vessel diameter. The optimal MSA cutoff value for LMCA lesions derives from IVUS studies on Asian populations with smaller anatomies and should be taken cautiously until further clinical data confirm their validity. What is more, the results are biased by the lack of a pre-procedural IVUS examination, a limitation acknowledged by the authors themselves [12].

By IVUS, optimal stent expansion for ostial and mid-shaft LMCA lesions is defined as a stent area of more than 90% of the distal reference lumen of the vessel, while in the setting of distal LMCA lesions, a stent area of more than 90% of the proximal reference vessel lumen is defined as optimal [13].

2.2. Incomplete stent apposition

Incomplete stent apposition refers to the separation of the stent struts from the vessel intima with evidence of blood behind the struts and without side branch involvement [38].

If stent apposition is difficult to obtain, minor residual degrees of incomplete apposition of less than 0.5 mm axial distance and less than 2mm in length as assessed by IVUS are considered acceptable [13]. Intravascular OCT also enables malapposition assessment in vivo with high accuracy. When the malapposition is less than 300μm most probably the struts and vessel will be in contact after endothelization, therefore postdilatation is only necessary in malappositions surpassing 300 μm [19]. Due to the tapering of the LMCA, stenting of distal LMCA and of an ostial branch lesion according to the distal reference diameter predisposes to significant malapposition in the proximal vessel. As a result, intracoronary imaging derived data are essential in the selection of an appropriate stent design [39].
2.3. Tissue prolapse

Tissue prolapse is an intraluminal tissue (plaque and/or thrombus) extrusion through the stent struts [40]. Its prevalence depends on the plaque composition (more frequent in stenting over TCFAs), stent design and clinical presentation [38]. IVUS detected tissue prolapse has been associated with poor short-term outcomes (more acute and subacute thromboses and no-reflow phenomenon). However, long-term outcomes were not different in patients with tissue prolapse after PCI in infarct related arteries [40]. OCT detects tissue prolapse two times more frequently than IVUS, with tissue prolapse occurring in up to 95% in deployed stents [38], which means that OCT also visualizes the minimal protrusions without clinical impact. However, tissue prolapse in LMCA stenting has yet unknown consequences, as literature data is currently missing.

2.4. Stent edge dissection

Stent edge dissection is an unplanned vessel tearing, occurring at the transition between the rigid stent struts and the adjacent arterial wall. It is caused by focal vessel barotrauma during stent implantation. Edge dissection appears as a linear rim of tissue with a clear separation from the vessel wall [41]. Deeper injuries are more likely to induce exposure of thrombogenic stimuli both in relatively normal adjacent non-stented vessel walls as well as in uncovered contiguous plaques [41]. In addition, deeper injuries are expected to induce stronger repair responses leading to stent edge restenosis.

Due to its high resolution, OCT detects numerous non-flow-limiting edge dissections, most of them being benign and without clinical consequences. Most studies have not shown a correlation between OCT-detected stent edge dissection and clinical events at one year, possibly because most OCT-detected edge dissections heal before midterm follow-up [37]. Nevertheless, large edge dissections may have a clinical impact. In non-LMCA procedures, the CLIO-OPCI II study showed that dissections >200 μm at the distal stent edge conveyed a higher risk of MACE, whereas proximal dissections had no clinical impact [36]. Another study found that deep vessel wall injury at stent edges with a dissection flap thickness more than 0.31mm carries an adverse impact on long-term clinical outcome [42]. ILLUMIEN III study classified edge dissections as major (≥60° of the circumference of the vessel at the site of dissection or ≥3 mm in length) or minor (any visible edge dissection <60° of the circumference of the vessel and <3 mm in length) [18]. In line with these data, some studies suggest that limited dissections that are angiographically “silent” and seen only by OCT, have a minimal impact on outcomes after stent deployment in the modern PCI era [38,43].

The impact of stent edge dissections in LMCA PCI is less studied. On one hand, the large diameter of LMCA and the increased blood flow is supposed to decrease the risk of acute thrombosis. However, in the case of an acute stent thrombosis or if restenosis should occur, the clinical result would be devastating. Therefore, the threshold for treating stent edge dissections in LMCA PCI should be probably lower.

2.5. Geographical miss

In addition to optimal stent apposition, the absence of dissection or intramural hematoma, plaque burden <40% at the stent edges defines the success of the PCI procedure, by IVUS assessment [13]. By automatically detecting the radiopaque marker of the optical lens in angiography, recent OCT machines are able to co-register OCT and angiography. This co-registration gives the operator the possibility to exactly position the stent in a precise landing zone, as identified by OCT. Studies are showing that in the absence of co-registration, the target plaque as indicated by OCT was not fully covered in 70% of cases [19].

The greater resolution of OCT as compared to IVUS, makes it suitable for the diagnosis of edge dissections, geographical miss, tissue prolapse, or residual thrombus, although many of these findings may have a benign course. In fact, despite a less clear clinical impact, OCT imaging has been shown to influence operator decisions, leading to additional interventions in up to half of the patients [4].

3. Intracoronary imaging in acute coronary syndromes with LMCA culprit lesion

In the setting of an acute coronary syndrome, intracoronary imaging identifies the culprit lesion, and defines lesion morphology and severity in the not so rare situation of angiographically ambiguous LMCA findings [44]. In addition, intravascular imaging provides additional prognostic information as compared to the classic clinical and anatomic risk factors [44,45]. The IVUS and OCT-defined plaque burden is a predictor of subsequent MACE, while the lipid-core burden index as determined by virtual histology IVUS is a predictor of plaque vulnerability and is associated with worse clinical outcomes [44]. Given the higher rates of stent thrombosis in ST-segment elevation myocardial infarction patients (0.8%) versus other patient cohorts (0.3% in non-ST-segment elevation acute coronary syndrome, and 0.1% in stable ischemic heart disease respectively), intracoronary imaging guidance of LMCA stenting could significantly improve clinical outcomes. However, the hemodynamic compromise which characterizes patient presentation in this acute setting, and the subsequent procedural emergency, exclude the use of intravascular imaging.
The use of intravascular imaging to identify vulnerable coronary plaques is the subject of on-going research. At present, its role in guiding stent deployment for subsequent “plaque sealing” of vulnerable plaques is purely hypothetical and should be avoided, both in the context of LMCA disease as well as in other non-LMCA lesions [46,47].

**Conclusion**

IVUS and OCT are the two main intracoronary imaging techniques used for lesion assessment and stent optimization in LMCA disease. IVUS is more user-friendly, inexpensive, and widely available. The details offered by OCT are superior to the ultrasonic evaluation, but the evidence supporting the use of IVUS in the setting of LMCA disease is more extensive and the cutoffs used for lesion severity are better defined. New guidelines are required to establish a generally accepted algorithm of anatomic assessment and procedural success evaluation in the high-risk and demanding field of LMCA percutaneous procedures.

**Conflict of interest:** none

**References**

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