REVIEW ARTICLE

Invasive assessment modalities of unprotected left main stenosis

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Among all coronary lesions, the decision-making process for the treatment of unprotected left main (ULM) stem lesions is still challenging. Indeed, the optimal therapeutic strategy for patients with ULM disease remains controversial: coronary artery bypass grafting was established as the gold standard, but it is without doubt that percutaneous coronary intervention (PCI) performed by experienced operators achieves good results at long term follow up, especially in cases where the ostium and/or shaft of ULM are treated. Thanks to the widespread use of invasive assessment of atherothrombotic ULM stenosis, improved selection of PCI cases and techniques of stenting, better outcomes are now possible. This review seeks to define the place of PCI in ULM disease by describing the different modalities of ULM stenosis assessment.

Keywords: Unprotected left main disease, Percutaneous coronary intervention, Coronary artery bypass graft, Intravascular ultrasound, Fractional flow reserve

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Introduction

Isolated unprotected left main (ULM) involvement is observed in 7% of coronary artery diseases (CAD), and in 13%, 17% and 27% of cases it is associated with single, double and triple vessel disease respectively [1,2]. The optimal therapeutic strategy for patients with ULM disease remains controversial. Although coronary artery bypass grafting (CABG) was established as the gold standard for treatment of patients with ULM disease [3], in the last decade, percutaneous coronary intervention (PCI) for this lesion subset is increasing, especially where the atherothrombotic disease is located at ostium and/or shaft of left main stem [4–11]. Indeed, for this type of lesion, PCI is associated with good long-term outcomes and may represent a valid alternative therapy to CABG [12,13]. Current European guidelines assign a Class IIb, Level of Evidence: B indication for PCI in patients with distal left main bifurcation, either isolated or with concomitant single vessel disease [14].

The rationale for use of intracoronary physiology assessment and imaging arises from the limitations of coronary angiography in determining the severity of coronary stenoses. The visual assessment of percent diameter reduction has significant inter-observer variability even among experienced interventional cardiologists [15].

In addition, the widespread use of invasive imaging modalities has determined a better understanding of the process, which can be related to restenosis and stent thrombosis, underlining the importance of an invasive assessment of ULM atherosclerotic plaque in order to choose the best strategy to adopt. This review tries to define the place of PCI in ULM disease and describes the different modalities of ULM stenosis assessment.

Abbreviations

CABG	= coronary artery bypass graft
CAD	= coronary artery disease
DES	= drug eluting stent
FD-OCT	= frequency-domain optical coherence tomography
FFR	= fractional flow reserve
IVUS	= intravascular ultrasound
MACCE	= major adverse cardiac
MLA	= minimal lumen area
MLD	= minimal lumen diameter
OCT	= optical coherence tomography
PCI	= percutaneous coronary intervention
QCA	= quantitative coronary analysis
ULM	= unprotected left main

CABG or PCI: a delicate choice

In an older study, Cohen and Gorlin [16] revealed that CABG improves 10-year survival when compared with medical therapy in patients with significant ULM stenoses. This finding was subsequently confirmed by several randomized trials [3]. Therefore, in clinical practice today, the gold standard of treatment for ULM stenosis is represented by CABG. Since the beginning of the angioplasty era, ULM PCI has represented an attractive target for interventionalists in relation to its relatively large diameter and proximal location (which do not determine technical problems related to deliverability of device). However, three anatomical features have a capital impact and need to be considered. First, isolated ULM stenoses are only observed in 7% of patients, whereas over 70–80% of patients also have multivessel CAD [2,3,16]. In such cases, CABG could be preferred in order to achieve a complete revascularization. Second, most ULM stenoses (40–94%) concern the distal segment of ULM [2,3,16]. Such bifurcated or trifurcated lesions have high procedural risks and present high rates of restenosis [3], and a possible acute occlusion (stent thrombosis) may have catastrophic consequences. Finally, the presence of calcification is common [17], leading to difficulties in stent expansion.

On the other hand, CABG may be associated with high risk of mortality in patients with co-morbidities in comparison with PCI [18]. Thus, for the correct choice of a revascularization strategy in case of ULM disease, the stratification of procedural risk is as imperative as a careful evaluation of the long-term benefits of both PCI and CABG. Several methods of stratifying risk in patients undergoing ULM revascularization are available. Risk scores can be divided into those using clinical-based parameters, those using angiographic variables, and those using a combination of both.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) [19] is an additive clinical score including 17 objective clinical variables. The utility of using the EuroSCORE in patients undergoing PCI has been evaluated in the SYNTAX study [20], and several additional non-randomized studies [21–23]. Additive EuroSCORE was shown to be an independent predictor of MACCE not only in patients with ULM disease undergoing PCI [22–24], but also in those undergoing CABG [22–23]. Rodés-Cabau et al. [24] found that in octogenarians EuroSCORE $\geqslant 9$ identified as the best predictor of major adverse cardiac and cerebral events (MACCE) after PCI and CABG at two-year follow up. A EuroSCORE > 5, commonly accepted as a high-risk surgical group [19], was also shown to be an independent predictor of death and myocardial infarction.

The Society of Thoracic Surgeons (STS) scale aims to accurately estimate peri-operative risk complications such as mortality, stroke, kidney failure, prolonged mechanical ventilation or infection [25]. Although it was only verified among surgical patients, it could be a useful diagnostic tool to choose the appropriate method of revascularization, if verified in the PCI LMD group [25,26]. Other clinical scores such as the ACEF score [27] and the Mayo Clinic risk score [28] have also been evaluated. No clinical score takes account of the presence and severity of LM disease except for the STS-score [25]. Table 1 provides an overview of the variables evaluated in the score systems.

Various scores based on angiographic data have been proposed. The SYNTAX score was first prospectively used in the SYNTAX trial and has since been used in different clinical trials, in both acute and elective patients [29,30]. The SYNTAX score has a capital role to play not only in stratifying clinical outcomes, but also in assisting important revascularization decisions in patients undergoing revascularization of ULM disease. In the ULM subgroup of the SYNTAX study, the SYNTAX score was an independent predictor of MACCE for patients undergoing PCI, but not for those undergoing CABG. At two-year follow up, in high SYNTAX score tertile (⩾32) patients, the MACCE rate was higher in the PCI group (29.7% vs. 17.8%, $p = 0.02$) [20]. This may be because the bypass anastomosis occurs distal to the complex disease. However, at four-year follow up, Farooq et al. [31] found a trend towards increased mortality in the high CABG SYNTAX score group (9.1% vs. 1.8% for low CABG SYNTAX score group; p = 0.084); and an increase in the composite MACCE (7.0% vs. 16.4%; $p = 0.126$).

The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularization address the indications for CABG compared with left main PCI in stable patients with lesions suitable for both procedures and low predicted surgical mortality [14]. These guidelines provide a Class IIa (Level of Evidence: B) recommendation for PCI of left main ostial or shaft disease when it exists in isolation or in combination with one-vessel disease; a Class IIb (Level of Evidence: B) recommendation for left main distal bifurcation disease when it exists in isolation or in combination with one-vessel disease; a Class IIb recommendation for any left main disease with concomitant two- or three-vessel disease and a SYNTAX score ⩽32; and a Class III recommendation for left main disease with concomitant two- or three-vessel disease and a SYNTAX score >32. CABG is the favored approach for all of these scenarios (Class I, Level of Evidence: A) [14]. The importance of considering both clinical and angiographic variables in the assessment of overall risk has led to the use of combined risk scores such as SYNTAX score II.

Indeed, SYNTAX score II provides an impartial, evidence-based assessment of the decision-making process for clinicians weighing anatomical and clinical factors to establish the optimum revascularization technique for individual patients with complex coronary artery disease. Such an instrument might help to more clearly and objectively define the often uncertain line that separates patients for whom PCI or CABG should be considered, as reported in appropriate-use criteria for coronary revascularization. This score should be used by heart teams consisting of a

Table 1. Summaries of variables evaluated in different clinical score systems.

	Euroscore	STS-score	ACEF score	Mayo clinic score
Age	x	x	x	x
Sex	x	x		
Ethny		x		
Body mass index		x		
COBP	x	x		
Peripheral arteriopathy	x	x		x
Neurological dysfunction	x	x		
Renal function	x	x	x	x
Previous cardiac surgery	x	x		
Clinical presentation	x	x		x
Left ventricular ejection fraction	x	x	x	x
Critical perioperative state	x	x		x
Operation related factor	x	x		
Left main disease		x		

clinical cardiologist, a cardiac surgeon, and an interventionalist to comply with international revascularization guidelines (Class 1 indication) [14], and to remove any possibility of individual bias in interpretation in order to select the safest and more efficient revascularization strategy.

In a large retrospective series of consecutive patients who underwent ULM PCI, Genereux et al. [32] confirmed the prognostic capability of the SYNTAX score II for mortality among patients with complex coronary artery disease. CABG preference based on SYNTAX score II was an independent predictor of mortality (HR = 4.13; 95% CI: 1.59–10.7; $p = 0.004$) after ULM PCI.

Finally, the ULM revascularization strategy should take into account patient preference and operator experience to achieve the optimal result.

Invasive assessment of ULM disease

Coronary angiography limits

Coronary angiography is still the standard tool for the assessment of coronary artery stenoses. While angiographic assessment of severe lesions is usually straightforward, the correct interpretation of intermediate lesions may be more challenging with a substantial inter-observer difference [33,34]. ULM anatomy, associated with vessel foreshortening and overlap, makes angiographic assessment difficult. Indeed, ostial left main lesions may appear more significant than they truly are, due to catheter-induced artifacts, whereas the severity of distal bifurcation lesions may be notoriously difficult to delineate accurately. Moreover, with only angiograms it is hard to delineate the correct understanding of plaque distribution at the bifurcation carina in case of distal ULM disease (Table 2).

It has been previously shown that prognosis in patients with ULM lesions that are non-functionally significant is favorable [35]. Moreover, CABG performed in non-hemodynamically significant lesions may lead to its early failure [36]. For all these reasons, a suspicious or borderline ULM lesion warrants further evaluation before either suggesting the need for revascularization or dismissing the need altogether [35–38].

Intravascular ultrasound

Several studies have shown that intravascular ultrasound (IVUS) is able to demonstrate significant left main disease in a very high percentage of angiographically normal patients [39–41]. Hermiller et al. [39] reported no correlation between IVUS and quantitative coronary angiography (QCA) lumen dimensions in patients with angiographically detectable left main disease. Many authors found that QCA underestimated the size of coronary vessels, and IVUS has been shown to detect LM disease that is angiographically silent [42,43].

Abizaid et al. [44] assessed the severity of left main stenosis in 122 patients by angiography and IVUS. Those patients did not have subsequent interventions and were followed up for one year to correlate angiographic and IVUS findings and identify predictors of subsequent coronary events. The event rate at one year was 14%. IVUS measurement of minimal lumen diameter (MLD) was the most important quantitative predictor of cardiac events. For any given MLD, the event rate was exaggerated in the presence of diabetes mellitus or an untreated lesion in a major vessel [44].

On the other hand, Fassa et al. [45] conducted IVUS studies on 214 patients with angiographically indeterminate ULM lesions. The lower range of normal ULM minimal lumen area (MLA) was 7.5 mm^2. Of the patients with angiographically indeterminate ULM, 38.8% had an MLA <7.5 mm^2, and 61.2% had MLA $\geqslant$7.5 mm^2. ULM revascularization was performed in 85.5% of patients with an MLA <7.5 mm^2 and deferred in 86.9% of patients with an MLA $\geqslant$7.5 mm^2. Long-term follow up showed no significant difference in major adverse cardiac events between patients with an MLA <7.5 mm^2 who underwent

Table 2. Comparison of different invasive assessment modalities.

	Angiograms	IVUS	Virtual histology	OCT	FFR
Quantitative analysis	++	+++	+	+	
Functional assessment	–	–	–	–	+++
Plaque composition identification	+	+++	+++	++	–
Vessel wall morphology identification	–	+++	+++	+	–
Identification of thronbus burden	+/–	+	+	+++	–
Evaluation of stenting result	+/–	++	+	+++	–
Evaluation of ostial ULM disease	+/–	+	+	–	–

IVUS intra vascular ultrasound; OCT optical coherence tomography; FFR fractional flow reserve; ULM unprotected left main.

revascularization and those with an MLA ⩾7.5 mm^2 deferred for revascularization [45]. Mintz [46] postulated that MLA <6 mm^2 makes the stenosis significant. He proposed another parameter crucial for ULM lesion significance: lumen stenosis higher than 50%. This approach, which is the most commonly used, may verify the ULM size and thus provide proper stenosis assessment, especially of a diffusely diseased vessel.

In a multicenter prospective study, de la Torre Hernandez et al. used a MLA of 6 mm2 as a cutoff value for deferring revascularization of the ULM [47]. In a two-year follow up period, no significant differences were observed between the deferred group and the revascularized group in cardiac death-free survival (97.7% vs. 94.5%; $p = 0.5$), and event-free survival (87.3% vs. 80.6%; $p = 0.3$) [47].

Although IVUS is not recommended for routine lesion assessment, current American guidelines assign to it a Class IIa, Level of Evidence: B indication in undetermined ostial ULM disease [48].

IVUS is also employed to evaluate results after ULM PCI especially in case of distal ULM treatment. Indeed, IVUS in ULM intervention is able to evaluate stent under-expansion, incomplete lesion coverage, small stent area, large residual plaque, and stent malapposition, which have been found to predict stent thrombosis after DES placement [49–50]. In the MAIN-COMPARE registry, Park et al. showed that elective stenting with IVUS guidance, especially in the placement of drug-eluting stents, may reduce the long-term mortality rate for unprotected left main coronary artery stenosis when compared with conventional angiography guidance. Non-randomized data reported that overall survival or event-free survival is improved when IVUS is used during ULM PCI [51].

In a cohort of 1670 patients, de la Torre Hernandez et al. showed association of IVUS guidance during PCI with better outcomes in patients with ULM disease undergoing revascularization with DES [52]. Indeed, IVUS-guided procedure was identified as a protective predictor for major adverse events in the overall population (hazard ratio = 0.70) and the distal ULM subgroup (hazard ratio = 0.54) [52].

In case of distal ULM treatment, IVUS may also play a role in the selection of the most appropriate stenting technique. Indeed, systemic use of a two-stent strategy, compared with a single-stent strategy, may increase the risk of stent thrombosis as well as repeat revascularization in bifurcation ULM lesions [53]. A better insight into plaque configuration with IVUS can diminish the unnecessary use of two-stent procedures by distinguishing true stenosis versus pseudo-stenosis caused by various artifacts, including the device, coronary spasm, or calcification at the side branch [54].

Ultrasound-based virtual histology

Greyscale IVUS is the gold standard modality for in vivo imaging of the vessel wall of the coronary arteries [55]. However, the greyscale representation of the coronary artery wall and plaque morphology associated with the limited resolution of current IVUS catheters makes it difficult to qualitatively identify plaque morphology similar to that of histopathology, which is the gold standard in characterizing and quantifying coronary plaque tissue components [56]. Innovative IVUS-based methods, such as virtual histology IVUS, based on interpretation of the raw radiofrequency analysis has been introduced [57–59]. Although this technique has been validated in vitro and ex vivo in human and animal models [57–60], results regarding its ability to qualitatively and quantitatively identify plaque components correctly remains controversial [61–63]. The main criticism stems from the fact that due to biological differences between animals and humans, the tissue types contained in animal atherosclerotic lesions may not be similar to the lesions seen in human disease. Other studies have compared virtual histology in human coronary arteries with other intra-coronary imaging techniques developed for the detection of necrotic core, finding a poor correlation [63,64]. Brugaletta et al. [63] showed that sensitivity and specificity of virtual histology for detection of necrotic core were both a modest 41.1% and 51%, respectively. Valgimigli et al. [65] employed IVUS-based virtual histology to study the plaque composition in left main stems. The authors found that the plaque necrotic content was minimal in the ULM, particularly in the most proximal tract, whereas it peaked in the first 6-mm segments after the ostium of the two major left coronaries. The length of ULM was shown to affect the distribution of necrotic core along the vessel. Indeed, in patients with long ULM, necrotic core content peaked immediately in the first coronary segment after the left main stem. Conversely, the necrotic core content peaked in the second 6-mm segment in patients with short left main stem and resulted in an increase in the two most distally analyzed segments compared to the long left main stem group [65]. Such findings confirmed the pathological studies results which have suggested that the so-called ''thin-cap atheromas'', necrotic-rich core plaques at high risk for rupture, are infrequent in the left main stem [66]. However, the benefits of the virtual histology technique in ULM assessment remains undetermined.

Optical coherence tomography

Optical coherence tomography (OCT) is an optical analog of intravascular ultrasound (IVUS) that can be used to examine the coronary arteries and has 10-fold higher resolution than IVUS. Indeed, OCT provides cross-sectional images with powerful resolution (10–20 μm) [67]. However, the first generation time-domain OCT systems had a relatively narrow field of view and required proximal vessel occlusion for image acquisition, precluding its application in ULM. Several studies have reported the safety and feasibility of the new frequency-domain OCT (FD-OCT) imaging in the clinical setting of non-ULM lesions [68–73]. Fujino et al. [74] employed FD-OCT to assess, guide, and monitor outcomes of PCI in ULM coronary disease, and showed a similar high safety and feasibility profile compared with IVUS both pre- and post-PCI. However, FD-OCT was associated with the use of additional iodine contrast and required more imaging pullbacks than IVUS [74]. Moreover, ostial ULM lesions are extremely challenging to assess with OCT.

Despite having established the clinical usefulness of IVUS, the literature is still lacking for OCT although this technique is currently limited by its penetration depth (1–3 mm) and its need for a blood cleared environment to obtain image production, it nonetheless appears to be a powerful imaging tool for the characterization of stent deployment in PCI. In fact, OCT enables the identification of a region of stent-strut malapposition that is unapparent angiographically. Following higher pressure and larger balloon inflation, OCT imaging showed optimal stent-strut apposition in great detail and without complications in its performance. Several case reports have been published about the management of ULM lesions using OCT [75,76]. Further multicentric randomized studies are necessary to investigate the real impact of OCT in ULM PCI.

Fractional flow reserve

The characteristics of fractional flow reserve (FFR) have been extensively described and validated over recent years [77,78]. FFR is a lesion specific index with unsurpassed sensitivity, specificity, and spatial resolution for the detection of inducible ischemia [79]. Its prognostic value for single and multi-vessel disease as well as left main disease has been demonstrated [80–83]. FFR was first validated using a cutoff value of 0.75. With further experience in the technique, investigators appreciated that by extending the cutoff value to 0.80, the sensitivity of FFR could be improved without greatly compromising the specificity. For this reason, a cutoff value of $\leqslant$0.80 was used in FAME 1 and FAME 2, and shown to be clinically valid [84]. However, FFR <0.75 is the effective cutoff for guiding revascularization decisions and evaluating intermediate ULM lesions [85].

Several caveats should be taken into account when using FFR for left main assessment. The method is indeed critically dependent not only on the anatomical characteristics of the lesion itself, but also on the vascular bed supplied by the left main trunk. The presence of a tight stenosis in one of the branches of the left main can also alter the pressure gradient across the left main, causing an overestimation of FFR if measured on the other branch [86]. Furthermore, if the right coronary artery is severely diseased or occluded and contralateral collateral flow is present, the vascular bed supplied by the ULM is increased. In this case, FFR may be reduced with a stenosis that would not be significant in the absence of the occluded vessel [87].

Jasti et al. [88] studied 55 ambiguous left main stenoses with IVUS as well as FFR and found that an IVUS MLA of 5.9 mm^2 or a minimal luminal diameter of 2.8 mm were predictive of FFR <0.75 with 93% sensitivity and 95% specificity [88]. Kang et al. [89] showed that an IVUS MLA of 4.8 and 4.1 mm^2 were predictive of an FFR value <0.8 and <0.75, respectively. All patients with an MLA >6 mm^2 had a negative FFR; 82% of patients with an MLA <4.8 mm^2 had an FFR <0.8. A high incidence of plaque rupture was found by IVUS (33%), and ruptured plaques had a lower FFR value than non-ruptured ones, even if the average MLA was not significantly different [89,90].

Conclusion

The optimal therapeutic strategy for patients with ULM disease is still controversial. An optimal result passes through rational risk stratification and better assessment of ULM stenosis. IVUS and FFR are two complementary modalities in ULM lesion assessment: FFR remains a simple and reliable tool to assess the functional significance of intermediate lesions in the presence of isolated ULM disease. However, IVUS is strongly preferred when other lesions are present. Both methods are useful to evaluate PCI final results. OCT also represents a valid alternative to assess stent apposition after ULM PCI.

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