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STATE-OF-THE-ART PAPER

CME

Contemporary Clinical Applications of Coronary Intravascular Ultrasound

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CME Objective for This Article: After reading this paper, the reader should be able to: discuss the strengths, limitations, and literature supporting the use of intravascular ultrasound as a tool assessing intermediate lesion severity; recognize the value and limitations of intravascular ultrasound for guiding bare-metal and drug-eluting stent deployment in left main, non-left main, bifurcation, chronic total occlusion, and saphenous vein graft lesions; and assess the potential of radiofrequency backscatter intravascular ultrasound for plaque characterization in the context of other future applications, such as multimodality imaging and high-frequency intravascular ultrasound in the catheterization laboratory.

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Contemporary Clinical Applications of Coronary Intravascular Ultrasound

Intravascular ultrasound (IVUS) provides valuable information on the coronary vascular lumen and wall and has been an important tool in the cardiac catheterization laboratory for over 2 decades. The major utility of IVUS relates to optimizing stent deployment, particularly in complex lesions. In percutaneous coronary intervention with bare-metal stents, IVUS guidance reduces restenosis. In percutaneous coronary intervention with drug-eluting stents, IVUS guidance may reduce rates of stent thrombosis with little affect on restenosis. The benefit of IVUS guidance is most important in complex lesion subsets, such as left main and bifurcation lesions, where studies suggest that IVUS guidance may reduce mortality. Whereas IVUS luminal area measurements have been used to assess intermediate lesion severity, recent studies have demonstrated that IVUS accurately identifies nonischemic lesions for which percutaneous coronary intervention can be safely deferred, but cannot accurately predict hemodynamically significant lesions and should not solely be used to justify revascularization. In the current review, we focus on clinical applications of IVUS in interventional cardiology. (J Am Coll Cardiol Intv 2011;4:1155–67)

With its excellent imaging quality and spatial resolution, intravascular ultrasound (IVUS) provides complementary diagnostic information to angiography regarding lumen and vessel dimensions, plaque burden and composition, and arterial remodeling. Indeed, IVUS can identify lesions in which revascularization can safely be deferred, guide therapeutic strategy in lesions requiring percutaneous coronary intervention (PCI), and assess stent deployment. In the current review, we focus on the clinical applications of IVUS with a focus on the recently published literature.

IVUS Principles

There are 2 types of IVUS systems for clinical use: the mechanical single-element rotating transducer and the solid-state electronic phased array transducer. The 6-F compatible mechanical systems offer a more uniform pullback and greater resolution due to the higher ultrasound frequency. Mechanical systems are available commercially as the 40-MHz iCross or Atlantis SR Pro catheters (Boston Scientific, Santa Clara, California), the Revolution 45-MHz catheter (Volcano Corp., Rancho Cordova, California), and the 40-MHz LipiScan IVUS (InfraReDx, Burlington, Massachusetts). The solid-state phased array transducer has 64 stationary transducer elements around the tip that image at 20 MHz, and it is commercially available as the 5-F–compatible Eagle Eye Catheter (Volcano Corp.). Benefits of the solid-state catheter include enhanced trackability due to the coaxial design and lack of nonuniform rotational distortion artifacts seen with rotational systems.

IVUS for Assessment of Angiographic Intermediate Lesions

A major limitation of coronary angiography is that it fails to accurately determine anatomy, as it produces a 2-dimensional representation of a 3-dimensional coronary lumen. In addition, diffuse reference vessel disease, lesion foreshortening, angulations, calcification, eccentricity, vessel overlap, and streaming of contrast can complicate angiographic assessment of lesion severity. As IVUS provides both accurate lumen and vessel dimensions, it is therefore not surprising that it has been shown to be more reproducible and accurate than angiography for assessment of atherosclerotic disease severity (1–3). Basic IVUS measurements for assessing lesion severity are illustrated in Figure 1.

Non–left main lesions. Management of intermediate lesions remains a therapeutic dilemma for interventional cardiologists. Even experienced interventional cardiologists cannot accurately assess the hemodynamic significance of intermediate or moderate lesions between 40% and 70% stenosis using angiographic assessment (1,3). In addition, significant inter- and intraobserver differences in angiographic interpretation of disease severity have been reported (1).

Even though fractional flow reserve (FFR) is considered the gold standard for intermediate lesion assessment (4–6), several studies have reported fairly good correlation between anatomic data by IVUS and ischemia by physiological assessments. In fact, FFR can be accurately predicted using established equations and accurate 3-dimensional IVUS imaging (7). Early studies suggested that minimal lumen area (MLA) $\geq$4 mm^2 by IVUS had a diagnostic accuracy of 89% in identifying a coronary reserve flow $\geq$2.0 (8), whereas an

MLA <4 mm^2 correlated well with ischemia on single-photon emission computed tomography (9). This cutoff value of an MLA <4 mm^2 also correlated moderately well with an FFR <0.75 in a study of 53 intermediate lesions from 43 patients, with a sensitivity and specificity of 92% and 56%, respectively (10). Additionally, low event rates were noted in 300 patients with intermediate lesions in whom intervention was deferred for an IVUS MLA ≥4 mm^2 (11). Based on these studies, many clinicians have used an MLA cutoff value of 4.0 mm^2 to determine if PCI was warranted.

However, the limitation of a single IVUS MLA cutoff is that the hemodynamic effects of a lesion are not only dependent on MLA, but also on numerous other factors, including lesion length, eccentricity, entrance and exit angles and forces, reference vessel dimensions, and the amount of myocardium subtended by the lesion. Not surprisingly, other studies have found different MLA values and a combination of other anatomic parameters to predict FFR. In a study of 51 patients with intermediate stenosis, the combination of an MLA <3 mm^2 and an area stenosis >60% best predicted FFR <0.75 (12). Recently, in an analysis of 236 intermediate lesions from 201 patients, the best cutoff value of MLA to predict an FFR <0.80 was 2.4 mm^2 (sensitivity of 90% and specificity of 60%) (13). Furthermore, in 92 intermediate lesions from 84 patients, MLA of <2.8 mm^2 and <3.2 mm^2 best correlated with an FFR <0.75 and <0.80, respectively (14). Finally, in 94 patients with intermediate lesions with smaller vessels (reference diameter <3.0 mm), the best predictors for FFR <0.75 were MLA ≤2.0 mm^2 (sensitivity of 82% and specificity of 81%), plaque burden ≥80% (sensitivity of 88% and specificity of 79%), and lesion length ≥20 mm (sensitivity of 64% and specificity of 79%) (15).

Taken together, these studies suggest that an MLA ≥4.0 mm^2 can accurately identify nonischemic lesions for which PCI can be safely deferred. By contrast, an MLA <4.0 mm^2 does not accurately predict a hemodynamically significant lesion and should not be used to justify revascularization. The significance of an MLA <4.0 mm^2 should be considered in the context of reference vessel size, lesion length, area stenosis, plaque burden, and area of myocardium at risk (13–15). Whereas FFR is the preferred tool for intermediate lesion assessment, an algorithm for contemporary IVUS-guided PCI of non–left main lesions is proposed in Figure 2.

Left main lesions. As revascularization with coronary artery bypass grafting, compared with medical therapy, for significant left main coronary artery lesions has been shown to reduce mortality, the accurate assessment of intermediate left main lesions is important to optimize outcomes (16). Furthermore, the angiographic assessment of stenosis severity in the left main is challenging, as this segment is short, often calcified, with diffuse disease involving the ostium or bifurcation (Fig. 3).

IVUS has been widely used in the assessment of intermediate left main coronary artery lesions (17). In a study of 55 patients with moderate left main stenosis, an MLA cutoff value of 5.9 mm^2 (sensitivity of 93% and specificity of 95%) and a minimal lumen diameter of 2.8 mm (sensitivity of 93% and specificity of 98%) best correlated with FFR <0.75 (18). Additionally, in 354 patients with intermediate left main stenoses, an MLA value >6.0 mm^2 identified patients at low risk for adverse events with deferred revascularization (19).

Meanwhile, other IVUS studies have defined significant left main lesions by different MLA cutoff values. Unpublished data from 47 patients with intermediate left main lesions suggested an MLA <4.5 mm^2 best correlated an FFR <0.80 (predictive accuracy 83%) (Seung-Jung Park, unpublished data, 2011). Furthermore, in 214 patients with intermediate left main lesions, an MLA ≥7.5 mm^2 was associated with good outcomes, whereas patients who were medically managed with an MLA <7.5 mm^2 had poor outcomes (20). Nevertheless, this nonrandomized observational study might have had confounding factors driving outcomes; therefore, definitive conclusions from this study are difficult regarding an MLA <7.5 mm^2.

Given the limitations of a single MLA to predict hemodynamic significance of a stenosis, FFR should be the preferred modality for intermediate left main lesion assessment. However, if IVUS is used, revascularization may be deferred in patients with left main MLA ≥6.0 mm^2 as these values are not associated with ischemia and have favorable outcomes. For an MLA <6.0 mm^2, consideration should be given to performing FFR or noninvasive stress testing before revascularization, as there may be discrepancy with the IVUS MLA cutoff (4.5 to 6.0 mm^2) that correlates with FFR (Fig. 4) (17–20).

Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
BMS = bare-metal stent(s)
CTO = chronic total occlusion
DES = drug-eluting stent(s)
FFR = fractional flow reserve
ISA = incomplete stent apposition
IVUS = intravascular ultrasound
MLA = minimal lumen area
MSA = minimal stent area
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

IVUS to Guide PCI

The major use of IVUS is to plan interventional strategy and optimize stent deployment. Pre-intervention IVUS accurately assesses reference lumen dimensions and lesion length for appropriate stent sizing. Additionally, identification of superficial calcium by IVUS can lead to pre-stent rotational atherectomy (American College of Cardiology/American

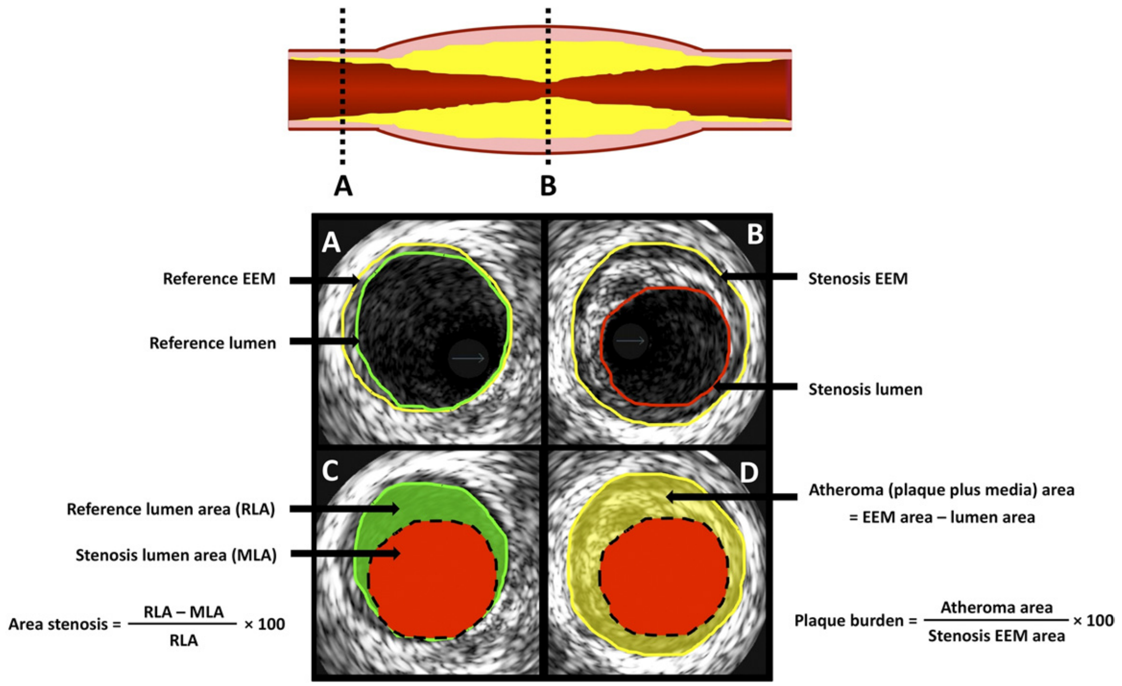

Figure 1. Basic IVUS Measurements

A is from the proximal reference, and **B** is from the most severe stenosis representing the minimal lumen area. **C** illustrates the calculation of area stenosis, which compares the stenosis lumen to the reference lumen. This is in contrast to plaque burden **(D)**, which compares the stenosis lumen to the stenosis external elastic membrane (EEM). Due to arterial remodeling, the plaque burden is not usually the same as area stenosis and therefore should not be used to assess stenosis severity. MLA = minimal lumen area; RLA = reference lumen area.

Heart Association [ACC/AHA] PCI guidelines, IIa indication) (21). Furthermore, when large thrombus burdens are detected by IVUS, operators may alter anticoagulant therapies or consider mechanical thrombectomy. Post-stent IVUS assessment may detect complications of PCI and suboptimal stent deployment and is supported by the ACC/AHA PCI guidelines (IIa indication) (21).

IVUS-guided PCI with BMS. Several IVUS characteristics have been associated with increased adverse events after PCI with bare-metal stent (BMS), including smaller minimal stent area (MSA), stent underexpansion, persistent edge dissections, incomplete stent apposition (ISA), and incomplete lesion coverage (22–27). Of these, smaller MSA is most commonly associated with target vessel failure at follow-up (26,28–32). In a registry of 1,706 patients, the risk of restenosis with BMS decreased 19% for every 1-mm^2 increase in MSA (31). Although studies have differed as to the best cutoff value for MSA (ranging from 6.5 to 9.0 mm^2), larger post-PCI areas consistently predict lower rates of restenosis (26,28–32). This is likely due to 2 major mechanisms. First, even in optimally deployed stents, smaller stents, compared with larger diameter stents, have greater restenosis rates, as similar amounts of neointimal hyperplasia leads to smaller lumen areas. Second, smaller MSA can represent stent underexpansion, which can be treated with appropriate post-dilation.

Stent underexpansion is defined as an area of inadequately expanded stent compared with the adjacent reference segment. Although, a consensus definition of adequate expansion is lacking, a simplified version of the MUSIC (Multicenter Ultrasound Guided Stent Implantation in the Coronaries) criteria can be used to define adequate expansion (>80% average reference cross-sectional area) (Table 1) (33). Most trials have used similar definitions and have favored an IVUS-guided PCI strategy with BMS over an angiography-guided strategy (24,34–40). An example of stent underexpansion is illustrated in Figure 5.

The clinical benefit of an IVUS-guided BMS PCI strategy is largely driven by reductions in restenosis and target vessel revascularization (TVR), without significant benefits in death or myocardial infarction. This was illustrated in a recent meta-analysis of 2,193 patients from 7 randomized trials, where an IVUS-guided PCI strategy with BMS reduced TVR (13% vs. 18%, $p < 0.001$) compared with angiography-guided PCI strategy with similar rates of death (2.4% vs. 1.6%, $p = 0.18$) and myocardial infarction (3.6% vs. 4.4%, $p = 0.51$) (41). The mechanism for the reduction in restenosis with IVUS-

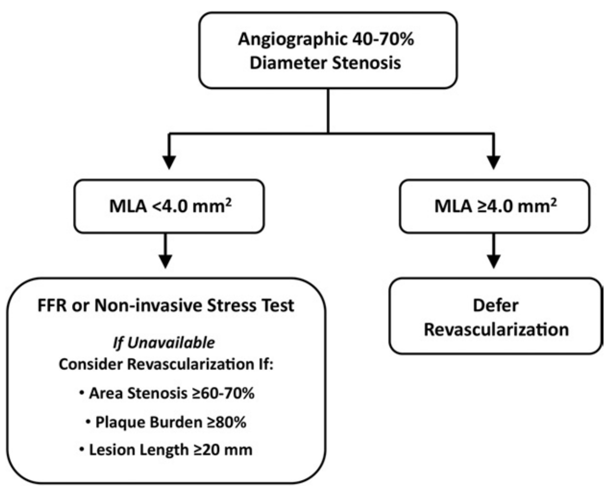

Figure 2. Proposed IVUS Criteria for Assessment of Intermediate Non–Left Main Coronary Lesions (40% to 70% Stenosis)

Invasive or noninvasive physiological evaluation is recommended to assess the significance of intermediate coronary lesions (4). In case intravascular ultrasound (IVUS) is used, the following is a proposed algorithm based on the recent literature (8–11,15). Most intermediate lesions with a MLA ≥4.0 cm^2 are nonsignificant and intervention may be safely deferred (8–11). For minimal lumen area (MLA) <4.0 mm^2, physiological evaluation is recommended. If physiological evaluation is unavailable, the significance of an MLA <4.0 mm^2 should be considered in the context of reference vessel size, lesion length, area stenosis, plaque burden, and area of myocardium at risk. Intermediate lesions are more likely to be hemodynamically significant in larger reference vessels when area stenosis is >60% to 70%, plaque burden is >80%, and lesion length is >20 mm (10,18). FFR = fractional flow reserve.

guided BMS PCI likely relates to the more frequent use of post-dilation with larger diameter balloons and at higher pressures, resulting in more adequately expanded stents with larger MSA (24,36).

Taken together, these studies suggest "bigger is better" in PCI with BMS, with the caveat that stent overexpansion and arterial overstretch might also induce arterial injury and has been associated with a higher degree of neointimal hyperplasia in several small studies (42,43).

IVUS-guided PCI with DES. RESTENOSIS. In contrast to the literature supporting an IVUS-guided strategy in PCI with BMS, studies evaluating IVUS guidance in PCI with drug-eluting stent (DES) have largely been limited to retrospective investigations, with no randomized controlled trials demonstrating improved clinical outcomes. A recent retrospective analysis of 250 patients undergoing PCI with DES showed no significant difference in restenosis with and without optimal stent expansion as defined by MUSIC criteria (44). The only published randomized trial to investigate an IVUS-guided strategy in PCI with DES, HOME DES (Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents with or without the IVUS Guidance) study, randomized 210 patients to an IVUS-guided PCI strategy versus an angiography-guided strategy (45). In this study, the IVUS-guided strategy led to more frequent post-dilations, higher balloon inflation pressures, and larger balloon sizes, but it did not result in lower rates of TVR or major adverse cardiac events. However, this study was considered underpowered to detect differences in clinical events. Moreover, the definition of optimal stent deployment was less rigorous than for other trials. Optimal stent deployment was defined as complete apposition of the stent struts, no edge dissections, and adequate stent expansion, which was defined as either MSA >5.0 mm^2 or >90% of the distal reference lumen area.

Similar findings were noted in the recently presented AVIO (Angiography Versus IVUS Optimization) study, which also compared IVUS-guided and angiography-guided PCI strategies with DES in 284 patients with complex lesions (long lesions, bifurcations, chronic total occlusions [CTO], and small vessels) (46). In AVIO, novel (and more aggressive) criteria for optimal stent deployment were used (Table 1). Although this IVUS-guided strategy led to larger stent dimensions, this did not translate into improved clinical outcomes at 9 months in this study. However, clinical follow-up was incomplete and the study was possibly underpowered to detect differences in restenosis.

STENT THROMBOSIS. Whereas IVUS-guided PCI in DES may not influence rates of restenosis, there is increasing evidence that this strategy may reduce rates of stent thrombosis. In a recent propensity-matched analysis of 884 patients undergoing PCI with DES, an IVUS-guided strategy was associated with reduced rates of stent thrombosis at both 30 days (0.5% vs. 1.4%, p = 0.046) and 12 months (0.7% vs. 2.0%, p = 0.014) when compared with an angiography-guided strategy (47). In addition, IVUS guidance was found to be an independent predictor of freedom from stent thrombosis. The mechanism of this benefit may be related to the identification and treatment of suboptimal stent deployment. Indeed, several studies have suggested that factors associated with stent thrombosis include edge dissections, stent underexpansion, ISA, incomplete lesion coverage, geographic miss, tissue protrusion, and residual thrombus (48–55). Of these IVUS findings, edge dissections, stent underexpansion, and ISA have been the most extensively investigated.

EDGE DISSECTIONS. Early after PCI, persistent higher-grade dissections on angiography classified as National Heart, Lung, and Blood Institute types B to F dissections have been associated with higher rates of acute thrombosis (22,56). Therefore, prolonged balloon inflations or deployment of a second stent are commonly used to treat these angiographically apparent higher-grade dissections. The incidence of persistent edge dissections by IVUS after DES implantation is approximately 10%, of which almost 40% are not detected by angiography (57). High-grade edge

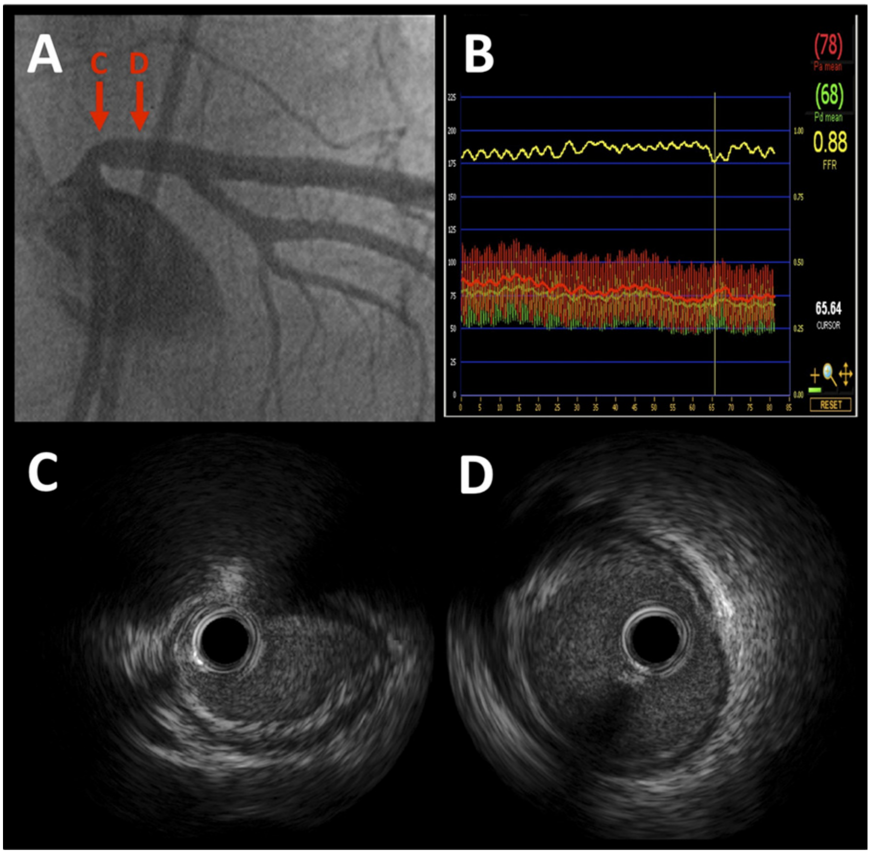

Figure 3. Angiographic Intermediate Ostial Left Main Lesion

An example of an angiographic intermediate ostial left main lesion **(A)** that was investigated by FFR **(B)** and IVUS **(C, D).** FFR was 0.88, and IVUS demonstrated mild plaque with significant negative remodeling resulting in an MLA of 8.9 mm^2. The **red arrows (A)** indicate the location of IVUS frames displayed in **C** and **D**. The patient was medically managed and revascularization was deferred. Abbreviations as in Figures 1 and 2.

dissections, defined by IVUS as lumen area narrowing <4 mm^2 or dissection angle $\geq 60°$, have been associated with higher rates of early stent thrombosis (55) and, therefore, should be stented. However, low grade and angiographically silent edge dissections may not be associated with higher rates of adverse events (57–59), and there is no consensus on their optimal management.

STENT UNDEREXPANSION. Smaller stent areas have consistently been associated with higher rates of stent thrombosis, implicating stent underexpansion in the pathogenesis of both early and late stent thrombosis. In 7,484 patients undergoing PCI with BMS, early thromboses were most commonly associated with inadequate post-procedure lumen area, either alone or in combination with dissection, thrombus, or prolapse (23). Similarly, several small studies in the DES era have demonstrated that stent underexpansion and smaller MSAs (usually <5.0 mm^2) are associated with early and late stent thrombosis. In 15 patients with early stent thrombosis after DES implantation, MSA (4.3 ± 1.6 mm^2 vs. 6.2 ± 1.9 mm^2, $p < 0.001$) and optimal stent expansion ($65 \pm 18\%$ vs. $85 \pm 14\%$ of reference lumen area, $p < 0.001$) were significantly lower than for a matched control group without thrombosis (50). Similar findings have been noted in other small series of patients with DES thrombosis (51,52). Based on these limited data, and until larger studies are performed, it seems reasonable to target optimal DES expansion defined similarly to BMS criteria ($>80\%$ average reference cross-sectional area).

ISA. ISA is defined as the absence of contact between the stent struts and the lumen wall and can occur acutely after stent deployment (acute ISA) or develop over time (late-acquired ISA). Acute ISA is almost always due to suboptimal stent implantation (Fig. 6). The frequency of acute ISA has been reported to be approximately 10% (60). Although, acute ISA is associated with variable rates of persistent ISA at follow-up (61,62), somewhat surprisingly, it appears not to be associated with increased cardiac events at 1 year (49,60,63,64).

There are mixed data regarding the risk of stent thrombosis associated with late ISA. Late ISA may either be due to persistence of acute ISA (late-persistent ISA) or the

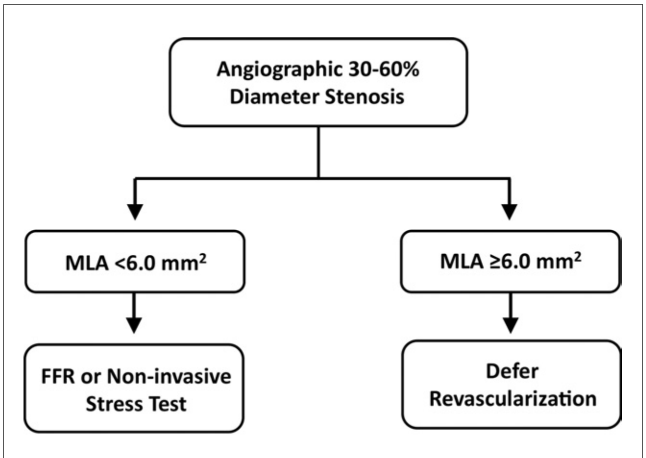

Figure 4. Proposed IVUS Criteria for the Assessment of Intermediate Left Main Coronary Lesions (30% to 60% Stenosis)

FFR remains the gold standard for the hemodynamic assessment of the intermediate left main lesions. However, if IVUS is used, it is reasonable to defer revascularization in patients with left main with an MLA ≥6.0 mm^2. For an MLA <6.0 mm^2, consideration should be given to performing FFR or noninvasive stress testing before revascularization as there may be discrepancy in the best IVUS MLA cutoff that correlates with FFR. Abbreviations as in Figures 1 and 2.

development of new ISA in regions that were previously apposed (late-acquired ISA) (Fig. 7). The mechanism for late-acquired ISA is thought to be related to either positive remodeling of the vessel, resolution of thrombus present at the time of the initial stent deployment, or delayed-type hypersensitivity reaction (48,65). The incidence of this late ISA has been shown to be 4 times more common in patients receiving DES versus BMS (54,66).

Several studies suggest that late ISA is associated with increased rates of stent thrombosis. In the initial study by Cook et al. (49), the rate of late ISA was significantly higher in patients with DES thrombosis than in control patients without stent thrombosis (77% vs. 12%, $p < 0.001$). However, segments with thrombosis were also associated with longer lesions, longer stents, more stents per lesion, lower stent expansion index, and more stent overlap, making definitive conclusions about the importance of late ISA in this setting difficult. Most recently, in a meta-analysis of 5 trials, patients with late ISA (n = 228) were associated with an increased risk of stent thrombosis compared with patients without late ISA (n = 1,852) (odds ratio: 6.51, 95% confidence interval: 1.34 to 34.91, p = 0.02) (54). By contrast, other studies have not found this relationship (60,63,64,66–68). In a pooled study of 1,580 patients enrolled in the IVUS substudies of multiple TAXUS stent trials, there were 36 cases of late-acquired ISA at 9-months follow-up, which were not associated with increased rates of stent thrombosis or major adverse cardiac events over the ensuing 2 years (60). In total, these studies suggest that at present, the results are inconclusive as to the relationship between ISA and long-term adverse outcomes in DES. Regardless, most operators would strive to achieve full apposition of all stent struts after stent deployment.

IVUS-guided PCI in unprotected left main lesions. In unprotected left main coronary artery PCI, the adverse consequences related to suboptimal stent deployment are more dramatic, and, as such, IVUS guidance may be of particular importance in this lesion subset. The largest study to date investigating IVUS guidance in left main PCI was the recently published propensity score matching analysis of 210 matched patients undergoing unprotected left main PCI from the multicenter MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) trial (69). In this analysis, there was a trend toward lower 3-year mortality with an IVUS-guided strategy versus angiography alone (6.0% vs. 13.6%, p = 0.063). Interestingly, in the 145 matched-patient subgroup receiving DES, the 3-year incidence of mortality was significantly lower in the IVUS-guided group (4.7% vs. 16.0%, p = 0.048). It has been postulated that the mechanism of benefit is related to reduced rates of sudden cardiac death related to late stent thrombosis. It should be noted that the risk of myocardial infarction and TVR were not influenced by IVUS guidance, and the mortality benefit was

Table 1. IVUS Criteria for Optimal Stent Deployment

MUSIC Criteria	AVIO Criteria
• Complete apposition of stent	• Minimal post-stent area >70% of the balloon cross-sectional area used to post-dilate the stent
• Adequate stent expansion MSA ≥90% of the average reference lumen area or ≥100% of reference segment with the lowest area when the MSA is <9 mm^2 or MSA ≥80% of the average reference lumen area or ≥90% of reference segment with the lowest area when the MSA is >9 mm^2	• The noncompliant post-dilation balloon size selected according to the average of the maximum and minimum media-to-media diameter at the following points: 1. Distal in-stent segment 2. Proximal in-stent segment 3. In-stent of maximal narrowing
• Symmetrical stent expansion Defined by minimum lumen diameter divided by maximum lumen diameter ≥0.7	

The criteria for optimal stent deployment used in the MUSIC (33) and AVIO (46) studies.
AVIO = Angiography Versus IVUS Optimization study; IVUS = intravascular ultrasound; MSA = minimal stent area; MUSIC = Multicenter Ultrasound Guided Stent Implantation in the Coronaries study.

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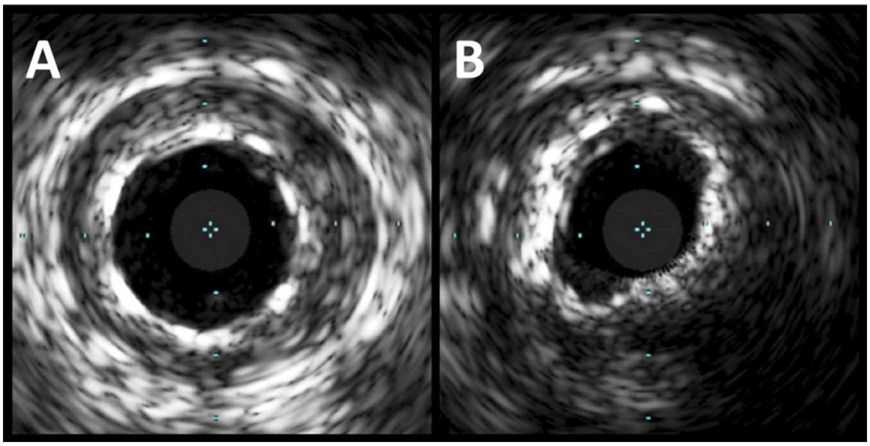

Figure 5. Stent Underexpansion

An example of stent underexpansion in the mid stent at an area of calcified plaque **(B).** The proximal stent illustrates symmetrical stent expansion **(A).**

not found in patients undergoing PCI with BMS. Overall, these data suggest that IVUS guidance is advocated for left main PCI with DES.

IVUS-guided PCI for bifurcation lesions. Pre-intervention IVUS can assist in the optimal selection of bifurcation PCI strategy, particularly by assessing plaque morphology and distribution at the side branch ostium. Currently, compared with routine 2-stent strategies, a single-stent strategy with provisional side branch intervention has become the favored approach for most bifurcation lesions due to reduced cardiac events (70). In a recent propensity-matched analysis of patients undergoing PCI of non–left main bifurcations with DES using predominantly a single-stent strategy, an IVUS-guided PCI strategy (n = 487) was associated with larger post-stent lumen diameters in both the main vessel and side branch than an angiography-guided PCI strategy was (n = 487) (71). Importantly, IVUS guidance was associated with lower rates of death or myocardial infarction than angiography guidance (3.8% vs. 7.8%, $p = 0.03$).

Pre-intervention IVUS of the side branch ostium may also be useful to predict the likelihood of side branch compromise due to plaque and/or carina shift after single-stent deployment in the main branch (72). Recently, in 90 bifurcation lesions, a pre-intervention MLA of $\geq$2.4 mm^2 in the side branch could accurately predict a nonischemic post-intervention FFR ($\geq$0.80) in the side branch (predictive value of 98%) after main branch stent deployment. However, an MLA $<$2.4 mm^2 could not accurately predict side branch compromise resulting in an ischemic FFR (predictive value of 40%).

At present, IVUS guidance is advocated in bifurcation lesion PCI with DES. If the pre-intervention side branch MLA is $\geq$2.4 mm^2, provisional side branch PCI can usually be deferred. However, if the side branch MLA is $<$2.4 mm^2, clinical judgment and/or side branch FFR should be considered to guide provisional side branch intervention.

IVUS-guided PCI for in-stent restenosis. In PCI for in-stent restenosis, IVUS can assist in the differentiation of restenosis related predominantly to intimal hyperplasia versus mechanical complications, such as stent fracture or stent underexpansion. An IVUS-guided high-pressure angioplasty with a noncompliant balloon is often performed when stent underexpansion is the major mechanism for restenosis to avoid deployment of a second stent, especially with DES restenosis. Balloon-alone angioplasty may also be appropriate in the presence of very focal lesions due to neointimal hyperplasia in both BMS and DES. In patients with diffuse or proliferative in-stent restenosis of either BMS or DES, a second DES is often warranted. The use of IVUS to guide PCI in patients with restenosis is supported in the ACC/AHA PCI guidelines (IIa indication) (21).

IVUS-guided PCI for CTO. In CTO, antegrade recanalization approaches often result in subintimal guidewire tracking. In small series, operators have used IVUS imaging from the false lumen to guide re-entry of the wire into the true lumen (73–75). Additionally, in a small series of 31 CTO lesions (of which 22 were previous failed attempts), successful recanalization was achieved in 100% of cases using a modified retrograde IVUS-guided approach (76). Regardless of approach, once the CTO is crossed, IVUS provides important information regarding reference vessel size, plaque distribution and composition, as well as the adequacy of stent deployment.

IVUS-guided PCI for saphenous vein graft lesions. IVUS guidance during saphenous vein graft PCI may be particularly important as saphenous vein grafts are often larger sized than native vessels, making angiographic size assessment more difficult. Indeed, oversized stents (stent to reference ratio $>$1.0) result in greater rates of periprocedural

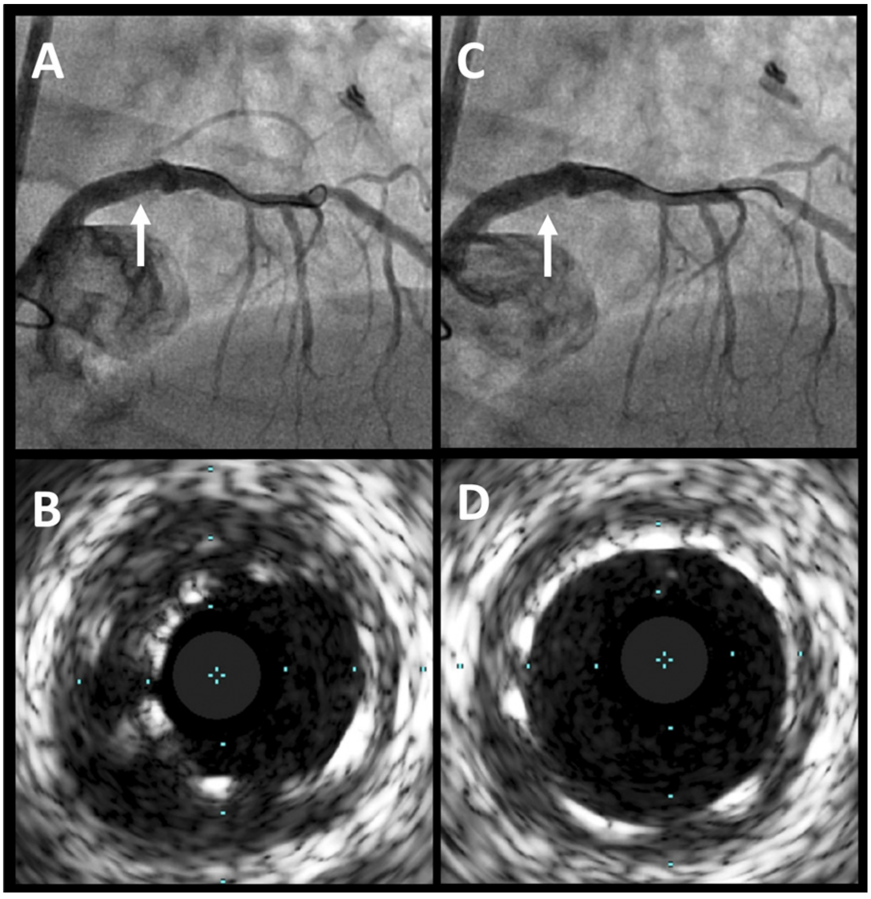

Figure 6. Acute Incomplete Stent Apposition

Angiogram **(A)** of an example of acute incomplete stent apposition found immediately post stent implantation by intravascular ultrasound (IVUS) **(B)** in the left anterior descending coronary artery of a patient, as well as the post-dilation angiography **(C)** and IVUS **(D)** of the same location.

myocardial necrosis and distal embolization without reducing 9-month revascularization rates (77,78). In addition, stent oversizing may result in graft perforation. Therefore, it is reasonable to use IVUS to select appropriately sized stents for saphenous vein graft PCI.

Radiofrequency IVUS

The addition of radio frequency backscatter signal analysis allows for improved characterization of plaque composition. Currently, there are 3 available software programs for plaque composition assessment: 1) virtual histology IVUS (VH–IVUS) (Volcano Corp.); 2) iMAP (Boston Scientific); and 3) Integrated Backscatter IVUS (IB-IVUS) (YD Co., Ltd., Nara, Japan). VH-IVUS has been compared with actual histology from directional coronary atherectomy specimens (79), coronary arteries from ex-planted hearts (80), and carotid endarterectomy section (81) with overall moderate predictive accuracies (80% to 94%). Similar validation studies have been performed for iMAP and IB-IVUS (82). Major limitations of the current radiofrequency-based IVUS imaging technologies include the inability to accurately detect thrombus and characterize plaque behind calcium due to acoustic shadowing (83). In addition, the accuracy of these 3 IVUS platforms to detect thin-cap fibroatheromas is limited by resolution, which does not allow for the detection of cap thickness <65 μm (82,84). In an ex vivo autopsy study, IB-IVUS provided higher diagnostic accuracy for tissue characterization than VH-IVUS (85).

The ability of the combination of grayscale IVUS and radio frequency backscatter analysis to predict the site of future coronary events was evaluated in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial (86). In PROSPECT, 697 patients presenting with acute coronary syndromes were enrolled and underwent PCI of all culprit lesions followed by 3-vessel VH-IVUS imaging. At 3-year follow-up, nonculprit VH-IVUS defined thin-cap fibroatheromas with a plaque burden ≥70% and MLA ≤4.0 mm^2 had an 18% major adverse cardiac events rate

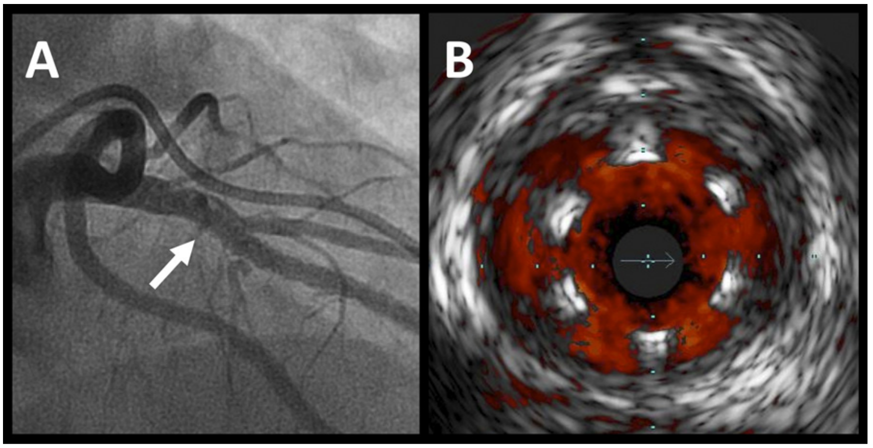

Figure 7. Late Incomplete Stent Apposition

Angiography **(A)** and IVUS **(B)** studies of an incomplete stent apposition using ChromaFlo in the proximal left anterior descending coronary artery of a patient presenting with an acute coronary syndrome. Although there was no baseline intravascular ultrasound (IVUS) at the time of stent deployment, the stent was likely undersized at the initial stent deployment and represents persistent incomplete stent apposition.

(driven largely by revascularization). The PROSPECT trial suggests that the addition of radio frequency backscatter analysis to grayscale IVUS might provide incremental prognostic information, but further studies are warranted to investigate this hypothesis. At present, PCI of nonsignificant lesions based on plaque composition alone is not justified.

Future Perspectives

In the near future, catheters with multiple imaging modalities may be combined for more comprehensive assessment of atherosclerosis. Optical coherence tomography has higher spatial resolution (10 to 12 μm) than conventional IVUS (120 μm) and might provide more detailed assessment of the lumen surface, including cap thickness and regional stent strut assessment (84). High-frequency IVUS catheters are also under development that may provide similar resolution to conventional optical coherence tomography. Other imaging modalities, such as near-infrared spectroscopy, have also been developed to detect lipid composition, and combined near-infrared spectroscopy and IVUS platforms have emerged. In addition, forward-looking IVUS systems are under investigation, which may assist in the percutaneous treatment of CTO (87).

Summary

Although, IVUS is not the imaging modality of choice for assessing intermediate lesion severity, it has an important role in guiding stent deployment, particularly for complex lesions such as bifurcations, left main, CTO, in-stent restenosis, and saphenous vein graft lesions. It is important for the clinicians to have a thorough understanding of the existing clinical applications of IVUS to best integrate novel imaging tools into clinical practice in the cardiac catheterization laboratory. Furthermore, new criteria specific to each novel imaging modality will have to be developed and validated before appropriate clinical application.

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